

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

-----X
In re: United States Patent
No. 4,634,697

#14
Attn: Box Patent Ext.

Inventor: Yoshio Hamashima

Issue Date: January 6, 1987
-----X

RECEIVED
FEB 12 1996
OFFICE OF PETITIONS
AND APPEALS

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

REQUEST FOR EXTENSION OF PATENT TERM UNDER
35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.785, Schering Corporation ("Schering") authorized agent (see Exhibit I) for Shionogi & Co., Ltd. ("Shionogi"), owner of the above-identified patent by virtue of an Assignment by Yoshio Hamashima of his interests in the above-identified patent which was executed on March 7, 1985 and recorded in the United States Patent and Trademark Office ("USPTO") on March 12, 1985 at Reel: 4383, Frames: 0597 to 0598 (Exhibit IX) hereby requests an extension of the 20 year from filing date patent term set pursuant to 35 U.S.C. § 154(c)(1) of United States Patent No. 4,634,697.¹

¹This request is proper under the October 16, 1995 Memorandum Opinion in Merck et al., v. Kessler, et al., U.S. District Court for the Eastern District of Virginia, Consolidated Nos. 95-CV-1005 et al. Schering recognizes that the Commissioner of Patents and Trademarks, the Commissioner of Food and Drugs, and the Generic Pharmaceutical Industry Association ("GPIA") have appealed to the United States Court of Appeals for the Federal Circuit to reverse the District Court's decision. Merck v. Kessler, Fed. Cir. Nos. 96-1108 et al. If the Federal Circuit adopts the position advanced in that case by the Commissioner of Patents and Trademarks and the Commissioner of Food and Drugs, then Schering requests an extension of the 17 year from issue term of United States Patent No. 4,364,697. If the Federal Circuit adopts the position advanced in that case by the Generic Pharmaceutical Industry Association in that case, then there is no need for Schering to

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.785 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAMES, PHYSICAL STRUCTURE OR CHARACTERISTICS:

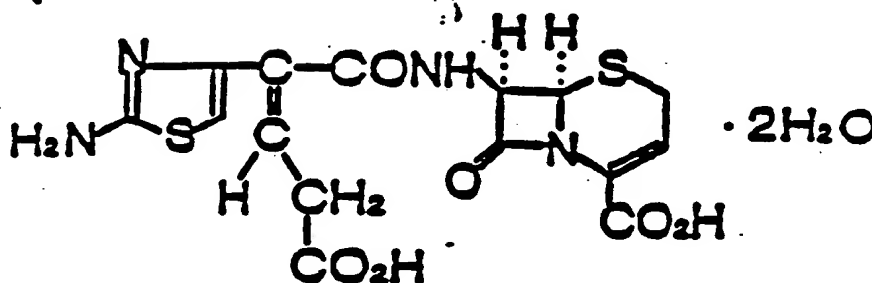
The approved product is CEDAX® (Ceftibuten for oral suspension). As used herein, the chemical name for the active ingredient in the approved product is ceftibuten which is present in the approved product as ceftibuten dihydrate. The active ingredient in the approved product has the following generic and chemical names and structural formula:

| | |
|----------------------|---|
| Generic Name: | Ceftibuten/Ceftibuten dihydrate |
| Code Designations: | 7432-S (Shionogi); and Sch 39720 (Schering) |
| CAS Registry Number: | CAS 97519-39-6 |
| Chemical Names; | |
| (1) | 5-Thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-, [6R-[6 α ,7 β (Z)]], dihydrate |

change its request for extension of the 20 year from filing term of United States Patent No. 4,364,697. Schering explicitly reserves the right to seek reconsideration and review of a USPTO determination to grant an extension of the 17 year from issue date term.

- (2) (+)-(6R,7R)-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, dihydrate.
- (3) 7β-[(Z)-2-(2-Aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid, dihydrate

Structural Formula



- (2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The regulatory review occurred under §507 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 357. Section 507 of FFDCA provides for the submission and approval of new drug applications ("NDAs") for antibiotic drug products meeting the definition of "antibiotic drug" under §507 of the FFDCA, 21USC §357(a)

- (3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR

USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

CEDAX® (ceftibuten for oral suspension) was approved by the FDA for commercial marketing on December 20, 1995 for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis in humans. (See Exhibits VII and VIII)

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT OR THE VIRUS-SERUM TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The active ingredient in the approved product, CEDAX® (ceftibuten for oral suspension) has the generic name of ceftibuten and the chemical names listed in Paragraph No. (1) hereinabove as well as in Exhibits II and VIII. The active ingredient, ceftibuten, approved for marketing under Section 507 of the FFDCA, has not previously been approved for commercial marketing or use under the FFDCA, The Public Health Service Act or the Virus-Serum Toxin Act.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR

SUBMISSION PURSUANT TO SEC. 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

The product was approved on December 20, 1995, and the last day within the sixty day period permitted for submission of an application for extension of the relevant U.S. Patent is February 18, 1996. February 18, 1996 is a Sunday and submission of this application is considered timely filed if submitted on or before February 20, 1996. This application is being timely filed before the expiration of the February 20, 1996 deadline, pursuant to 35 USC §21(a) and (b) and 37 CFR §1.7 and 1.741(a).

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO. 4,634,697

INVENTOR: YOSHIO HAMASHIMA

DATE OF ISSUE: JANUARY 6, 1987

FILING DATE: OCTOBER 1, 1984

EXPIRATION DATE: OCTOBER 1, 2004

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS), AND DRAWINGS:

A copy of the patent is attached as Exhibit III.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers or certificates of correction were filed for U.S. Patent No. 4,634,697. United States Patent No. 4,634,697, has not been re-examined and, as such, no re-examination certificate has been issued.

A copy of the receipt of the first maintenance fee statement (mailing date July 17, 1990) is attached as Exhibit XA. A copy of the second maintenance fee statement (mailing date May 6, 1994) paid on April 18, 1994 by Shionogi and good through January 6, 1998 is attached hereto as Exhibit XB.

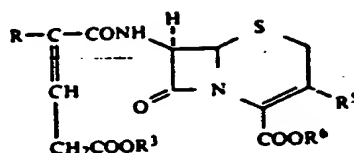
(9) A STATEMENT THAT THE PATENT CLAIMS, THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

Claims 1-3, 17 and 18 of United States Patent No. 4,634,697 read on CEDAX® (ceftibuten for oral suspension) for the FDA approved indication for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media, pharyngitis and tonsillitis. See the paragraphs in the Product Information Sheet entitled "Description" (upper left hand column and "Dosage and Administration" (upper right hand

column) and "Indications and Usage" (lower right hand column) (Exhibit VIII).

Claim 1 of United States Patent No. 4,634,697 reads

A compound of the formula



wherein

R is 2-aminothiazol-4-yl the amino group of which is unprotected or protected with a protecting group,

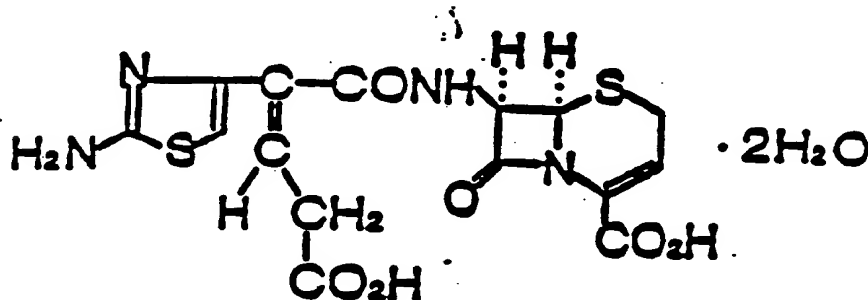
R³ is (1) hydrogen, (2) a pharmacologically acceptable salt forming group, (3) phthalidyl, (4) phenacyl, (5) C₂₋₇alkenyl, (6) diphenylmethyl, (7) trityl, (8) phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy or (9) a lower alkyl group,

R⁵ is hydrogen, methyl, vinyl, cyanovinyl, trifluoropropenyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, thiadiazolylthiomethyl, triazolylthiomethyl, aminomethylthiadiazolylthiomethyl, aminothiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio, or halogen, and

R⁶ is (1) hydrogen, (2) a pharmacologically acceptable salt forming atom or group, (3) a lower alkyl group, (4) a lower alkenyl group (5) phthalidyl, (6) phenacyl, (7) diphenylmethyl, (8) trityl or (9)

phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy.

The below-listed structural formula for ceftibuten dihydrate, the active ingredient in CEDAX® (Ceftibuten for oral suspension is set forth in paragraph 1 (page 2) hereinabove and on page 1, of Exhibit VII.) See also Product Information Exhibit VIII upper left hand column.



Thus claim 1 covers ceftibuten and ceftibuten dihydrate wherein R³, R⁵ and R⁶ are each hydrogen and R is 2-aminothiazol-4-yl, the amino group of which is unprotected.

Claim 2 reads:

A compound according to claim 1 wherein

R³ is hydrogen or a pharmacologically acceptable salt forming group,

R⁵ is hydrogen, methyl, vinyl, trifluoropropenyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, thiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio, or halogen, and

R⁶ is hydrogen or a pharmacologically acceptable salt

forming atom or group.

Thus, claim 2 covers ceftibuten and ceftibuten dihydrate wherein R³, R⁵ and R⁶ are each hydrogen.

Claim 3 reads:

A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid.

Claim 3 specifically covers ceftibuten and ceftibuten dihydrate. See chemical names in paragraph 1 herein above, and specifically chemical name (3).

Claim 17 reads:

An antibacterial composition which comprises an antibacterially effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier therefor.

Claim 17 covers ceftibuten and ceftibuten dihydrate for reasons stated in reference to claim 1 and in that the Cedax® (ceftibuten for oral suspension) is a pharmaceutical composition approved by the FDA for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis each of which are due to bacterial agents. See Product Information Sheet under paragraphs entitled "Dosage and Administration" and "Indications and Usage" (right hand column) of Exhibit VIII.

Claim 18 reads:

A method for combatting bacteria which comprises bringing an antibacterially effective amount of a compound of claim 1 into contact with the bacteria.

Claim 18 covers ceftibuten and ceftibuten dihydrate for the reasons stated in reference to claims 1 and 17.

(10) A STATEMENT BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A NEW DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

Schering of Kenilworth, New Jersey is the authorized agent of Shionogi by virtue of the appointment of agent (Exhibit I) to Schering. Shionogi is the assignee of record of United States Patent No. 4,634,697 by virtue of the Assignment dated March 7, 1985 by Yoshio Hamashima of his interest in U.S. Patent No. 4,634,697 (Exhibit IX) recorded in the USPTO on March 12, 1985 at REEL: 4383, FRAMES: 0597 to 0598.

In furtherance of the need for an approved NDA, Schering, on August 25, 1988 submitted to the FDA, a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under §505 of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent NDA for the use of ceftibuten Sch 39720 oral-suspension in humans. The

Schering letter transmitting the IND to the FDA is attached as Exhibit IV. By a letter dated September 6, 1988, the FDA acknowledged receipt of the IND and assigned the IND No. 32,024. A copy of this FDA letter is attached as Exhibit V. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) as September 29, 1988, the effective date of an investigational exemption under §505 of the FFDCA.

Schering submitted a New Drug Application (NDA) for CEDAX® (ceftibuten for oral suspension) in humans on December 20, 1991. A copy of this Schering letter transmitting the NDA is attached as Exhibit VIa. By a letter dated January 7, 1992, the FDA acknowledged receipt of the NDA submission dated December 20, 1991 and assigned the submission NDA No. 50-686. A copy of this FDA letter is attached as Exhibit VIb.

By a letter dated December 20, 1995 (copy attached as Exhibit VII) the FDA advised Schering that the NDA No. 50-686 for use of CEDAX® (ceftibuten for oral suspension) in humans for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis in humans was approved effective on December 20, 1995.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i), the "testing phase" began on September 29, 1988, the date of the IND No. 32,024 effective and ended on December 20, 1991, the date the NDA No. 50-686 was initially submitted by Schering for use of CEDAX® (Ceftibuten for oral suspension) in humans under §505 of the FFDCA. And, for purposes of determining the "approval phase" of the "regulatory review period" under 35

U.S.C. §156(g)(1)(B)(ii) the "approval phase" began on December 20, 1991, the date the NDA No. 50-686 was initially submitted by Schering to the FDA and ended on December 20, 1995, the date on which the NDA No. 50-686 was approved by the FDA.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE ACTIVITIES UNDERTAKEN BY SCHERING, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

During the applicable regulatory review period, Schering was actively involved in obtaining FDA approval for the use of the CEDAX (ceftibuten for oral suspension) for the treatment of Pharyngitis and otitis media and urinary tract infections in humans. As previously noted, Schering submitted an IND on August 25, 1988 and in close consultation with the FDA conducted clinical trials from September 29, 1988 through December 20, 1991 under IND No. 32-024. Schering submitted on December 20, 1991 NDA No. 50-686 for the use of CEDAX® (ceftibuten for oral suspension) for the treatment of Pharyngitis and otitis media and urinary tract infections in humans. From December 20, 1991 to December 20, 1995 Schering continued to interact with various FDA officials and answered numerous questions, generated requested data and supplied requested information regarding all clinical studies and data on the use of CEDAX® (ceftibuten for oral suspension) for the treatment of Pharyngitis and otitis media and urinary tract infections in humans worldwide to obtain health approval. A brief description of the significant activities undertaken by Schering with respect to the use of CEDAX® (ceftibuten for oral suspension) for the treatment of Pharyngitis and otitis media and urinary tract infections in humans during the regulatory review period is set forth in Exhibit XI (IND) and Exhibit XII (NDA) and is illustrative of the activities involved.

(12) A STATEMENT BEGINNING ON A NEW PARAGRAPH THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR AN EXTENSION AND A STATEMENT AS TO THE LENGTH OF THE EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in the relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 USC §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Publ. 103-465, 108 Stat. 4809 (1994) and 35 U.S.C. §156, the term of United States Patent No. 4,634,697 currently expires on October 1, 2004. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 4,634,697.

(2) The term of this patent has never been extended under 35U.S.C. §156(e)(1).

(3) This application is being submitted by Schering Corporation, by virtue of the appointment of agent to Schering Corporation by Shionogi, the owner of record of this patent (Exhibit I). Shionogi is the owner of record by virtue of the Assignment by Yoshio Hamashima of his interest which was recorded in the USPTO on March 12, 1985 at Reel: 4383, Frames: 0597 to 0598 (copy attached as Exhibit IX). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on December 20, 1995, the date the product received permission for marketing under the FFDCA and ending on February 20, 1996 and contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 20, 1995 letter from the FDA (Exhibit VII), to Schering-Plough Corporation (of which Schering Corporation is a wholly owned subsidiary), the product was subject to a regulatory review period under §507 of the FFDCA before its commercial marketing or use.

(5) Finally, the CEDAX® (ceftibuten for oral suspension) oral suspension product was approved by the FDA for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis. The permission for the commercial marketing of CEDAX® (ceftibuten for oral suspension) after regulatory review under §507 of FFDCa, 21 U.S.C. §357, is the first permitted commercial marketing and use under §507 for humans of the active ingredient cefitbuten in CEDAX® (ceftibuten for oral suspension). This is confirmed by the absence of any approved new drug application for the active ingredient in humans prior to December 20, 1995.

(b) Statement as to length of extension claimed:

The 20 year from filing term of United States Patent No. 4,634,697 now expiring on October 1, 2004 should be extended by 1,826 days (5 years). This extension was determined on the following basis. As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of the IND No. 32,024 of September 29, 1988 and the submission of the NDA on December 20, 1991 a period of 1,074 days, plus the length of time between the submission of the NDA on December 20, 1991 to NDA approval on December 20, 1995, a period of 1,461 days. These two periods added together equal 2,535 days.

Pursuant to the introduction of 35 U.S.C. §156(c), the term of the patent eligible for extension shall be extended only for that portion of the regulatory review period which occurs after the date the patent is issued. In this case, no limitation under the introduction to §156(c) applies in that the

issue date of United States Patent No. 4,634,697 (January 6, 1987) is before the date on which the regulatory review period began.

Section 156(c)(2), requires the period calculated under §156(g)(1)(B)(i) to be reduced by one-half of the 1,074 day period; this reduction results in a value of 537 days.

From the foregoing calculation, an extension of 1,998 days results, i.e., the period under 35 U.S.C. 156(g)(1)(B)(i) as limited by §156(c)(2) (801 days) plus the period under 35 U.S.C. 156(g)(1)(B)(ii) (1,461 days). This extension period is subject to two further potential limitations under §156.

First, under §156(g)(6)(A), a maximum extension of five years is permitted. Since the calculated extension (1,998 days) is more than five years (1,827 days), this limitation does apply (the patent issued on January 6, 1987, which was after the enactment of §156 in 1984).

Second, under §156(c)(3), if the period remaining in the term of the patent after the date of approval, that is, December 20, 1995, to October 1, 2004, when added to the extension period calculated above would exceed 14 years, the period of extension would be limited so that the total does not exceed 14 years. In this case, however, the total of the remaining term (3,209 days) plus the five year extension (1,826 days) is 5,036 days and does not exceed the 14 year (5113 days) limit, and the extension is not reduced.

Accordingly, United States Patent No. 4,634,697 is eligible for 5 year or a 1,826 day extension from October 1, 2004 to October 1, 2009.

Schering's request for extension of term of 20 years from application filing date for United States Patent No. 4,634,697 is proper under the October 16, 1995 Memorandum Opinion in Merck et al., v. Kessler, et al., U.S. District Court for the Eastern District of Virginia, Consolidated Nos. 95-CV-1005 et al. Schering recognizes that the Commissioner of Patents and Trademarks, the Commissioner of Food and Drugs, and the Generic Pharmaceutical Industry Association ("GPIA") have appealed to the United States Court of Appeals for the Federal Circuit to reverse the District Court's decision. Merck v. Kessler, Fed. Cir. Nos. 96-1108 et al. If the Federal Circuit adopts the position advanced in that case by the Commissioner of Patents and Trademarks and the Commissioner of Food and Drugs, then Schering requests an extension of the 17 year from issue term of United States Patent No. 4,634,697. In that event, United States Patent No. 4,634,697 would be eligible for a five year (1827 day) extension from January 6, 2004 to January 6, 2009.

(13) A STATEMENT ON A NEW PAGE THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

Schering acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

As stated in Paragraph No. (9) hereinabove, Schering asserts that claims 1-3, 17 and 18 of United States Patent No. 4,634,697 embrace the approved product, the CEDAX® (ceftibuten for oral suspension) and its use for the approved indication and usage of said approved product.

The term of United States Patent No. 4,634,697 has never been extended. A copy of this patent is attached as Exhibit III.

(14) PRESCRIBED FEES:

The Commissioner is authorized to charge our Deposit Account No. 19-0365 in the amount of \$1,060.00 or any other fee necessary for this application to prevent it from becoming inadvertently abandoned.

(15) THE NAME, ADDRESS AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THIS APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED TO:


THOMAS D. HOFFMAN
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1- 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NEW JERSEY 07033-0530
TEL. NO. (908) 298-5037
FACIMILE NO. (908) 298-5388

(16) CERTIFICATION THAT THE ENCLOSED DUPLICATE COPY
OF THIS APPLICATION IS A TRUE COPY OF THE ORIGINAL:

I, Thomas D. Hoffman, Registration No. 28,221, as duly appointed attorney (by virtue of the following Power of Attorney duly executed by James R. Nelson, Vice President for Schering) for Applicant, Schering Corporation, authorized agent (by virtue of the Appointment of Agents, see Exhibit I) for the owner of record of United States Patent No. 4,634,697 by virtue of the aforesaid Assignment, see Exhibit (IX) which has applied for an extension of term of this patent, declare that the duplicate copy of this application transmitted herewith is a true copy of the original application.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of United States Patent No. 4,634,697.

Date: 02/09/96


Thomas D. Hoffman
Attorney for Authorized Agent
Registration No. 28221
Tel. No. (908) 298-5037

**(17) DECLARATION AND POWER OF ATTORNEY BY
AUTHORIZED AGENT**

As the below identified official of Schering Corporation, the authorized agent for the owner of record of United States Patent No. 4,634,697, which has applied for an extension of term of this patent, I declare (1) that I have been authorized to practice before the United States Patent and Trademark Office; and (2) that I have general authority from Schering Corporation, the authorized agent of the owner of record, to act on behalf of the owner of record in patent matters.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and United States Patent No. 4,634,697.

POWER OF ATTORNEY: I hereby appoint as United States attorneys and with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Thomas D. Hoffman, Reg. No. 28,221; John J. Maitner, Reg. No. 25,636; Norman C. Dulak, Reg. No. 31,608; Edward H. Mazer, Reg. No. 27,573; Eric S. Dicker, Reg. No. 31,699, and Richard J. Grochala, Reg. No. 31,518.

Send correspondence to:

Thomas D. Hoffman
Schering-Plough Corporation
Patent Dept., K-6-1-1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
Tel. No. (908) 298-5037

Date: February 9, 1996

By: James R. Nelson
James R. Nelson
Vice President,
Schering Corporation
Reg. No. 27,929


(17) DECLARATION FOR EXTENSION OF UNITED
STATES PATENT NO. 4,634,697

I, THOMAS D. HOFFMAN, Registration No. 28,221, as duly appointed attorney by virtue of the Power of Attorney duly executed by James R. Nelson Vice President of Schering Corp. for Applicant, Schering Corporation, the authorized agent for Shionogi (virtue of the Appointment of Agent, see Exhibit I), the owner of record of United States Patent No. 4,634,697 (by virtue of the aforesaid Assignment see Exhibit IX) which has applied for an extension of term of this patent, declare that (1) I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,634,697; (2) that I believe that the patent is subject to extension under 35 U.S.C. §156 and 37 C.F.R. §1.710; (3) that I believe that the length of extension claimed for the 20 year from filing date term specified in paragraph 12(A) is fully justified pursuant to 35 USC §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Publ. 103-465, 108 Stat. 4809 (1994) and 35 U.S.C. §156 and the applicable regulations; and (4) that I believe that the patent for which an extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and 37 C.F.R. §1.720.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may

jeopardize the validity of this application and any extension of United States
Patent No. 4,634,697.

Date: 02/09/96



Thomas D. Hoffman
Attorney for Authorized Agent of Record
Reg. No. 28,221
Tel. No. (908) 298-5068

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

-----x
In re: United States Patent
No. 4,634,697

Inventor: Yoshio Hamashima

Issue Date: January 6, 1987
-----x

: Attn: Box Patent Ext.

RECEIVED

: **FEB 12 1996**

OFFICE OF PETITIONS
: ~~ADMINISTRATIVE~~

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

**LETTER OF TRANSMITTAL OF APPLICATION FOR
EXTENSION OF PATENT TERM**

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,634,697 and a duplicate of the papers thereof, certified as such.

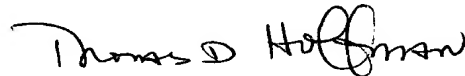
Also submitted herewith is an additional original declaration for extension of U.S. Patent No. 4,634,697. Therefore, the present application is complete and entitled to a filing date of 02/12/96.

Applicant, Schering Corporation ("Schering") states that Schering is the authorized agent for Shionogi and Co., Ltd., ("Shionogi") owner of U.S. Patent No. 4,634,697, (see Exhibit I); that Schering is the holder of the regulatory approval granted with respect to the regulatory review period for CEDAX® (ceftibuten for oral suspension) oral suspension as evidenced by: (1) submission on August 25, 1988 by Schering of IND

No. 32,024 to the Food and Drug Administration ("FDA") for the purpose of conducting clinical studies for the use of Ceftibuten (Sch 39720) powder for oral suspension in humans (see Exhibit IV); (2) the submission on December 20, 1991 by Schering of NDA No. 50-686 for CEDAX® (ceftibuten for oral suspension) (see Exhibit VIa); and (3) the FDA letter dated December 20, 1995 approving NDA No. 50-686 for CEDAX® (ceftibuten for oral suspension) for the treatment of acute bacterial exacerbations of chronic bronchitis and acute bacterial otitis media and pharyngitis and tonsillitis in humans (see Exhibit VII).

The Commissioner is hereby authorized to charge payment in the amount of \$1,060.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0365. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



Thomas D. Hoffman
Registration No. 28221
Attorney for Assignee of Record
Telephone No. (908) 298-5037

SCHERING-PLOUGH CORPORATION
Patent Department K-6-1-1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

EXHIBIT I

Appointment of Agent

Whereas Shionogi & Co., Ltd., (hereinafter "Shionogi") a company organized and existing under the laws of Japan, having its principal office in Osaka, 541 Japan and having an address currently designated as 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541, Japan and formerly designated as 12, Doshomachi 3-chome, Higashi-ku, Osaka 541, Japan, is the owner of record of U.S. Patent No. 4,634,697, entitled "Carboxyalkenamidocephalosporins," which was granted on January 6, 1987, by virtue of an Assignment of such U.S. Patent to Shionogi recorded on March 12, 1985, Reel 4383, Frame 0597;

Whereas Schering Corporation (hereinafter "Schering"), a corporation organized and existing under the laws of the State of New Jersey, U.S.A., with its principal offices at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033; has entered into an agreement with Shionogi under which Schering was granted certain rights under U.S. Patent 4,634,697;

Whereas Schering is desirous of marketing product containing a compound within the scope of the claims of U.S. Patent 4,634,697 including the product known as CEDAX (Ceftibuten for Oral Suspension);


Whereas Schering received marketing approval on December 20, 1995 from the United States Food and Drug Administration to market CEDAX (Ceftibuten for Oral Suspension) (NDA #50-686);

Whereas 35 USC §156, entitled, "Extension of Patent Term," provides at Section (a) (3) that an application for extension of a patent term be submitted by the owner of record of the patent or its agent;

Now, therefore, as the below-identified official of Shionogi I state that (1) I have been authorized to obligate Shionogi to sign this Appointment of Agent and (2) I hereby appoint Schering, its subsidiaries and/or its designees as agents of Shionogi for the express purpose of submitting and handling all matters and correspondence in the U.S. Patent and Trademark Office attendant to the application for extension of the term of U.S. Patent 4,634,697 covering CEDAX Oral Suspension pursuant to 35 USC §156. This appointment shall be co-extensive with the term of the aforesaid agreement between Shionogi and Schering.

Shionogi & Co.,Ltd.

Date: January 18, 1996

By: 

Name: Yoshihiko SHIONO
(type in name)

Title: Representative Director

S

EXHIBIT II

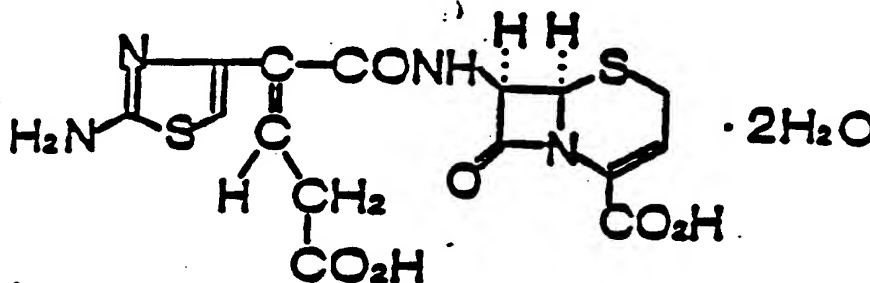
Drug Substance Summary

- 1.a. Description including physical and chemical characteristics and stability.**
Ceftibuten is a third generation cephalosporin antibiotic. A summary of pertinent information is provided in this section.

(1) (i) Nomenclature and Code Designation

| | |
|----------------------|--|
| Generic Name: | Ceftibuten |
| Code Designation: | 7432-S; Sch 39720 |
| CAS Registry Number: | CAS 97519-39-6 |
| Chemical Names: | (1) 5-Thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]-amino]-8-oxo-, [6R-[6 α , 7 α (Z)]], dihydrate (2) (+)-(6R, 7R)-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, dihydrate |

(ii) Structural Formula



Molecular Formula $C_{15}H_{14}N_4O_5S_2 \cdot 2H_2O$

Molecular Weight 446.43

(2) Physical and Chemical Characteristics

| | |
|-------------|--|
| Appearance: | White to yellowish white crystalline powder |
| Solubility: | Insoluble in water, hexane, chloroform, ethyl acetate and diethyl ether; very slightly soluble in acetone, methanol and anhydrous ethanol; freely soluble in dimethylformamide and dimethyl sulfoxide. Very slightly soluble between pH 1 and 4, slightly soluble between pH 5 and 8, sparingly soluble between pH 9 and 10. Solubility increased relative to water because of pH and/or ionic strength. |

| | |
|------------------------|---|
| pH (20-60 µg/mL): | 4.1-4.5 (decreases with increase in concentration) |
| pKa ₁ | 2.17 (4-carboxyl Group of the Cephem Ring) |
| pKa ₂ | 3.67 (Carboxyl Group on side chain of Blactam ring) |
| pKa ₃ | 4.07 (Aminothiazole Group) |
| Partition Coefficient: | Octanol/water partition coefficient is 0.040. |
| Specific Rotation: | $[\alpha]_D^{20} = +143^\circ$ to $+153^\circ$ (C=6 mg/mL, 0.1M phosphate buffer, pH 8.0) |
| TGA/DTA: | Ceftibuten loses water of adsorption -45°C, loses water of crystallization -60°C, decomposes -235°C |
| Polymorphism: | No polymorphs observed as evidenced by infrared spectroscopy, powder x-ray diffraction, and TGA/DTA. |
| Structure Elucidation: | Nuclear magnetic resonance spectroscopy, infrared spectroscopy, mass spectroscopy, and other analytical data in conjunction with the known chemical synthesis confirm the assigned structure. |
| Hygroscopicity: | Slightly hygroscopic between 50% and 90% relative humidity (RH) and dehydrates below 20% RH. |

1.a.(3) Ceftibuten Drug Substance
Stability Report Summary

Proposed Retest Dating

The proposed retest dating for Ceftibuten Drug Substance is 18 months when stored in double polyethylene bags in fiber or steel drums at or below -20°C.

Summary of Stability Studies

A report containing stability data obtained for Ceftibuten Drug Substance is provided. The stability conditions used for these studies are -20°C, 5°C, 15°C, RT (ambient temperature), 40°C, 25°C/75% RH, 25°C/90% RH, 40°C/75% RH, 10000-lux white light at 25°C.

Batch numbers, stability packaging and amount of stability data provided are summarized below.

| BATCH NUMBERS | STABILITY DATA PROVIDED | PACKAGING |
|--------------------------------------|---|---|
| 4X803 4X804 4Y805 | Up to 27 months (shorter for accelerated studies) | These batches of drug substance were stored in stoppered glass bottles for the 5°C, to 40°C conditions. Samples stored at RH or LT conditions were placed in open glass containers. |
| 88ZC03 88ZC04 88ZC05 88ZC06 | Up to 18 months (shorter for accelerated studies) | |
| 886006 886007 886010 | Up to 18 months | Polyethylene Bag (720 ± 9 mm wide, 1510 ± 20 mm long, and 0.10 ± 0.02 mm thick) made of low-density polyethylene (LDPE) virgin sheets which are doubled and placed in fiber drums. |
| 893004 893005 893006 | Up to 18 months at -20°C | |

The tests performed to evaluate the stability of ceftibuten (Sch 39720) drug substance are: Description (Physical Appearance), Specific Rotation, Moisture, Assay (HPLC), Related Substances - I, Related Substances - II (Group X compounds).

Summary of Results

The physical appearance of samples stored at 15°C or less for up to 27 months remains within specification (white to yellowish white). Discoloration to a yellowish brown occurs after 12 months at RT and even sooner at elevated temperatures and/or humidity conditions.

Specific rotation values decrease upon degradation of ceftibuten. The change in specific rotation is observed to parallel a decrease in drug substance potency and to provide a satisfactory control of optical purity.

Samples stored at all conditions were observed to remain within moisture specification (8.0 to 12.5%) for up to 27 months. No increasing or decreasing trends in the data are apparent with time.

The potency of ceftibuten decreases appreciably with time when stored at 5°C or higher. At 5°C the rate of loss is about 2 to 3% per year. An increase in relative humidity is also observed to further enhance the degradation rate. Exposure to light produces about a 4 to 5% loss of ceftibuten in 4 weeks. Ceftibuten samples stored in polyethylene bags inside of fiber drums and stored at -20°C are within specifications after 18 months. This storage condition has been selected for batches of drug substance so as to provide the highest possible purity of ceftibuten for formulation into products.

Both Group I and Group II Related Substances increase with a decrease in ceftibuten potency and good mass balance is generally observed. Related Substances I remain within specification ($\leq 3.0\%$) when stored at 5°C or less for up to 24 months. Related Substances II (Group X compounds) and the Total Related Substances remain within specification ($\leq 3.0\%$ and $\leq 4.0\%$, respectively) when stored at -20°C for up to 18 months.

Additional Studies

Stability studies on ceftibuten drug substance are ongoing. The packaging for the drug substance has now been upgraded to consist of an inner low density polyethylene bag closed with a plastic tie, an outer laminated polyethylene/polyvinylidene chloride/nylon bag containing an oxygen absorber closed with a plastic tie, and a gasketed steel drum. Further stability studies are planned using a comparable container/closure system.

1.b. Site of Manufacture and Control Operations

Manufacturing and control operations for the drug substance, ceftibuten dihydrate, will be performed at:

Shionogi and Company, Ltd.
Kanegasaki Plant
7, Moriyama, Nishine, Kanegasaki-cho
Isawagun, Iwate 029-45, Japan

Type I DMF 9297

In addition, control operations for the drug substance will also be performed at:

Schering Corporation
13900 N. W. 57th Court
Miami Lakes, Florida 33014

A letter of certification from Shionogi has been included to confirm that the above procedures will be conducted in accordance with the documentation included in this NDA and the above referenced DMF.

Alternatively, manufacturing operations for the intermediate, benzyloxycarboxamide or prenyl half ester will be performed by:

Katsura Chemical Company, Ltd.
Yamagata Plant
5850-1, Koh, Higashine, Higashine-Shi
Yamagata, 999-37 Japan

Type I DMF 9298

Included is a letter of confirmation from Katsura to confirm that all procedures will be carried out in conformance with the procedures contained in this NDA and the above referenced DMF.

2. Drug Product

| | <u>Page</u> |
|---|--------------------|
| a. Composition and Dosage Form | 02 0046 |
| b.(1) Manufacturer | 02 0048 |
| (2) Method of Manufacture | 02 0048 |
| c. Specifications & Analytical Methods | 02 0049 |
| d. Container/Closure System | 02 0054 |
| e. Stability | 02 0055 |
| f. Investigational Formulations | 02 0060 |

2.a.

Application Summary

Drug Product Composition and Dosage Form

Ceftibuten Powder for Oral Suspension

18mg/mL

18 mg/ml

Approximate
mg/g

| | |
|--|------|
| Ceftibuten | 72* |
| Polysorbate 80 NF | 0.4 |
| Simethicone, Food Grade | 0.8 |
| Xanthan Gum NF | 16 |
| Silicon Dioxide NF | 10 |
| Titanium Dioxide USP | 18 |
| Sodium Benzoate NF | 8 |
| Cherry Flavor, Natural & Artificial | 3.66 |
| Sucrose, Confectioners 6X (without starch) | |
| q.s. to make | 1 g |

***As ceftibuten dihydrate**

The drug product is a light yellow to buff colored powder.

Requisite amounts of powder are filled into appropriate glass bottles with a child resistant closure. When constituted with the designated amount of water, the requisite formula will yield a light yellow suspension containing 18 mg/ml Ceftibuten.

2.a.

Application Summary

Drug Product Composition and Dosage Form

Ceftibuten Powder for Oral Suspension
36mg/mL

| | <u>36 mg/ml</u> |
|--|-----------------------------------|
| | <u>Approximate</u> <u>mg/g</u> |
| Ceftibuten | 144* |
| Polysorbate 80 NF | 0.4 |
| Simethicone, Food Grade | 0.8 |
| Xanthan Gum NF | 16 |
| Silicon Dioxide NF | 10 |
| Titanium Dioxide USP | 18 |
| Sodium Benzoate NF | 4 |
| Cherry Flavor, Natural & Artificial | 3.66 |
| Sucrose, Confectioners 6X (without starch) | |
| q.s. to make | 1 g |

*As ceftibuten dihydrate

The drug product is a light yellow to buff colored powder.

Requisite amounts of powder are filled into appropriate glass bottles with a child resistant closure. When constituted with the designated amount of water, the requisite formula will yield a light yellow suspension containing 36 mg/ml Ceftibuten.

2.b.(1) Site of Manufacture, Packaging and Control Operations

Manufacturing, processing, packaging and control operations for the drug dosage form are performed at the Schering facilities at 13900 N.W. 57th Court, Miami Lakes, Florida, 33014.

2.b.(2) Drug Product Method of Manufacture

18 mg/ml and 36 mg/ml Products

The sugar is milled and portions blended with the xanthan gum, polysorbate 80, simethicone, silicon dioxide, sodium benzoate and titanium dioxide. The blend is added to the balance of the milled sugar with the ceftibuten* and blended. The batch is then mixed with the cherry flavor. The batch is packaged using appropriate packaging materials.

*As the dihydrate.

I. A. DESCRIPTION

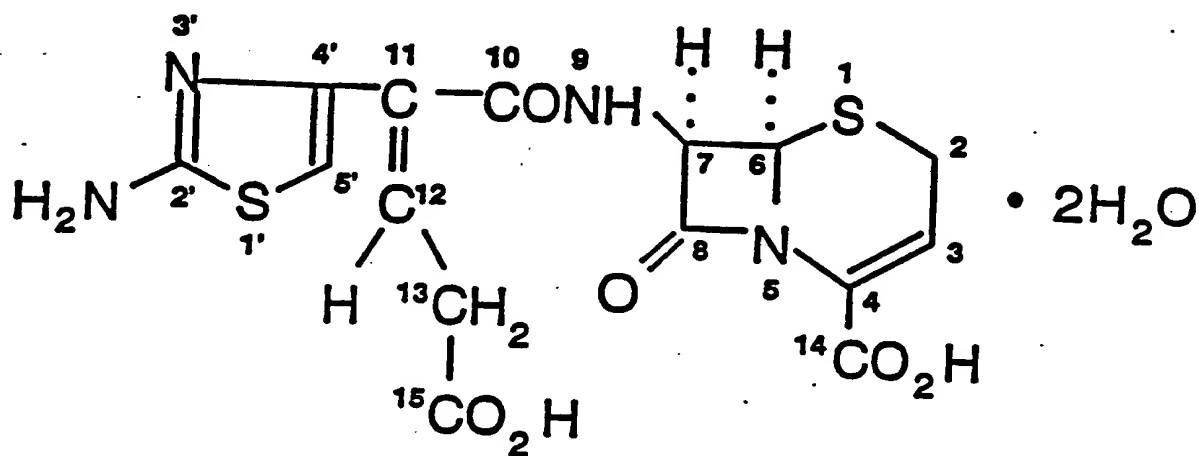
3. STRUCTURE ELUCIDATION OF CEFTIBUTEN

I.A.3.

TABLE OF CONTENTS
STRUCTURE ELUCIDATION OF CEFTIBUTEN

| | <u>Page(s)</u> |
|---|----------------|
| 1. Structure, Molecular Weight, Molecular Formula | 03 0052 |
| 2. Elemental Analysis | 03 0053 |
| 3. Proton Nuclear Magnetic Resonance Spectrum | 03 0054 |
| 4. Carbon-13 Nuclear Magnetic Resonance Spectrum | 03 0055 |
| 5. Mass Spectrum | 03 0057 |
| 6. Infrared Spectrum | 03 0058 |
| 7. Ultraviolet Spectrum | 03 0059 |
| 8. Absolute Configuration | 03 0060 |
| 9. Conclusion | 03 0061 |

1. Structure, Molecular Weight, Molecular Formula



Molecular Weight: 446.43

Molecular Formula: $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_6\text{S}_2 \cdot 2\text{H}_2\text{O}$

Refer to this figure when observing NMR signal assignments on the following pages.

2. Elemental Analysis

Table 1 lists the results of elemental analysis for 3 lots of cefitibuten. The values determined by analysis agree well with values calculated by taking total moisture (water of crystallization and water of adsorption) into consideration.

Table 1: Elemental Analysis

| Elements | Lot No. | | | | | |
|----------|---------------------------------|--------------|---------------------------------|--------------|---------------------------------|--------------|
| | 4X803 | | 4X804 | | 4Y805 | |
| | Calculated* ¹ (%) | Detm. (%) | Calculated* ² (%) | Detm. (%) | Calculated* ³ (%) | Detm. (%) |
| C | 38.46 | 38.77 | 39.21 | 39.12 | 38.65 | 38.85 |
| H | 4.40 | 4.42 | 4.26 | 4.33 | 4.36 | 4.40 |
| N | 11.96 | 12.17 | 12.19 | 12.30 | 12.02 | 12.18 |
| S | 13.69 | 13.97 | 13.96 | 13.92 | 13.76 | 13.91 |

*1 is calculated using a moisture content of 12.39%.

*2 is calculated using a moisture content of 10.67%.

*3 is calculated using a moisture content of 11.92%.

3. Proton Nuclear Magnetic Resonance Spectrum

The characteristic signals are assigned as shown below.

| Chemical Shift δ (ppm) | Number of Proton | Assignment |
|---|---------------------|-------------------|
| 3.22 (d, $J=7.4$ Hz) | 2 | 13-H ₂ |
| 3.57, 3.64 (ABq-d, $J=1.9, 6.5, 19.0$ Hz) | 2 | 2-H ₂ |
| 5.12 (d, $J=5.0$ Hz) | 1 | 6-H |
| 5.82 (dd, $J=5.0, 7.9$ Hz) | 1 | 7-H |
| 6.29 (s) | 1 | 5'-H |
| 6.48 (dd, $J=1.9, 6.5$ Hz) | 1 | 3-H |
| 6.49 (t, $J=7.4$ Hz) | 1 | 12-H |
| 7.08* (s) | 2 | NH ₂ |
| 9.34* (d, $J=7.9$ Hz) | 1 | 9-H |
| 12.78* (br) | 1 | 15-H |

* Exchanged with deuterium

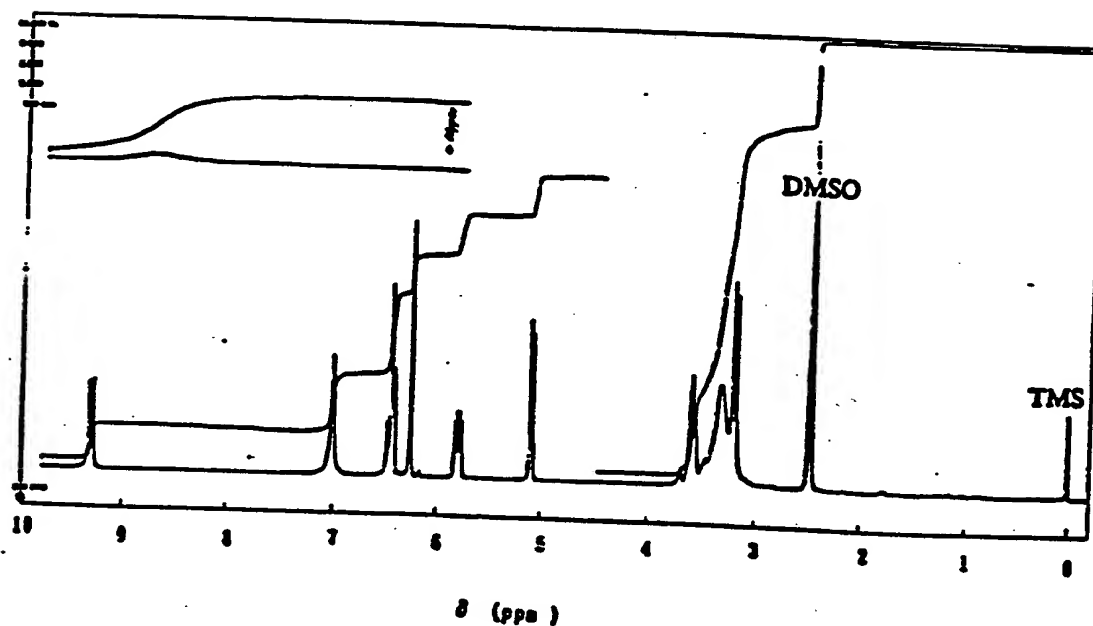


Figure 1: Proton Nuclear Magnetic Resonance Spectrum of Cefitibuten (Lot 4XB04) in d_6 -DMSO

4. Carbon-13 Nuclear Magnetic Resonance Spectrum

The characteristic signals are assigned as shown below.

| Chemical Shift δ (ppm) | Number of Linked Proton | Assignment |
|----------------------------------|----------------------------|------------|
| 23.6 | 2 | |
| 34.3 | 2 | |
| 56.9 | 1 | |
| 59.4 | 1 | |
| 103.5 | 1 | |
| 120.1 | 1 | |
| 123.6 | 1 | |
| 127.9 | 1 | |
| 133.4 | 0 | |
| 146.8 | 0 | |
| 162.6 | 0 | |
| 163.5 | 0 | |
| 167.5 | 0 | |
| 167.7 | 0 | |
| 172.0 | 0 | |

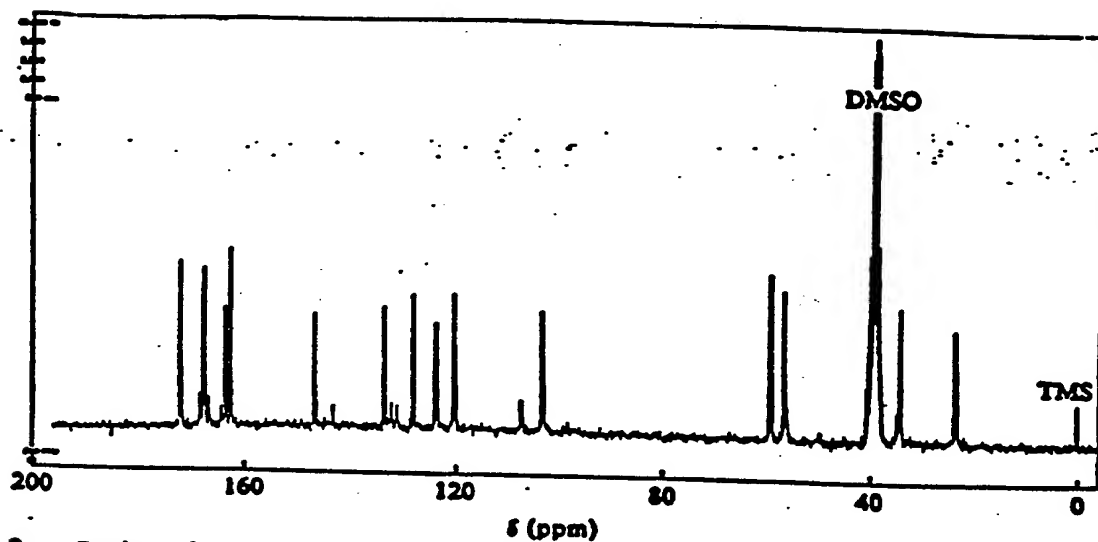


Figure 2: Carbon-13 Nuclear Magnetic Resonance Spectrum of Ceftibuten (Lot 4X804) in d_6 -DMSO

The ^{13}C -NMR spectrum shows that ceftibuten has the cis structure at the C_{11} - C_{12} double bond. The long-range coupling constant ($^3J_{\text{C-H}}$) between C_4 and 12-H is 6.1 Hz and that between C_{10} and 12-H is 11.4 Hz in the ^{13}C -proton non-decoupled spectrum of ceftibuten as shown in Figure 3. This means that the 12-H is closer to C_4 than it is to C_{10} . Therefore, ceftibuten is the cis form.

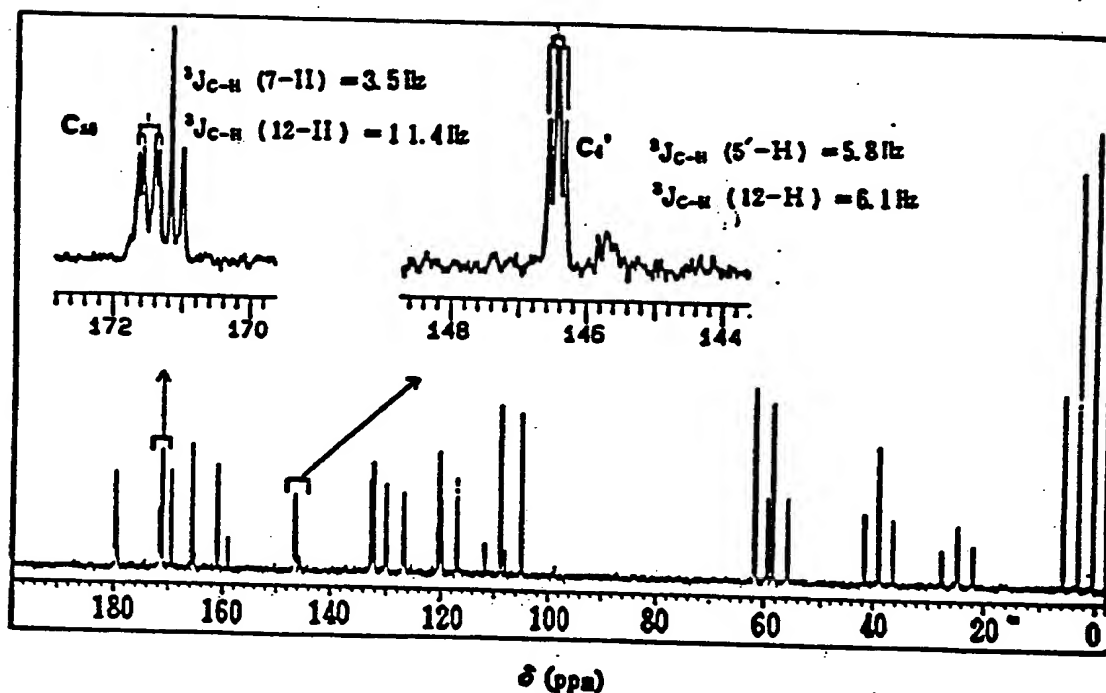
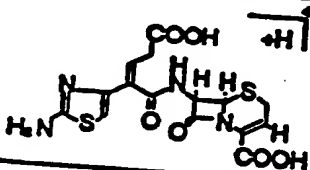
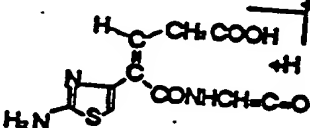
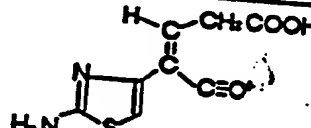
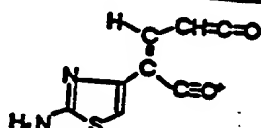


Figure 3: ^{13}C -Proton-non-decoupling Spectrum of Ceftibuten (Lot 4X804)

5. Mass Spectrum

The liquid secondary ion mass spectrum (SIMS) of ceftibuten was determined using dimethylsulfoxide as a solvent, and glycerol as a matrix. The characteristic fragment ions greater than m/z 190 are assigned as shown below.

| Fragment | Assignment |
|--------------|--|
| m/z 411 |  |
| 367 | $[MH \text{ minus } CO_2]^+$ |
| 268 |  |
| 211 |  |
| 193 |  |

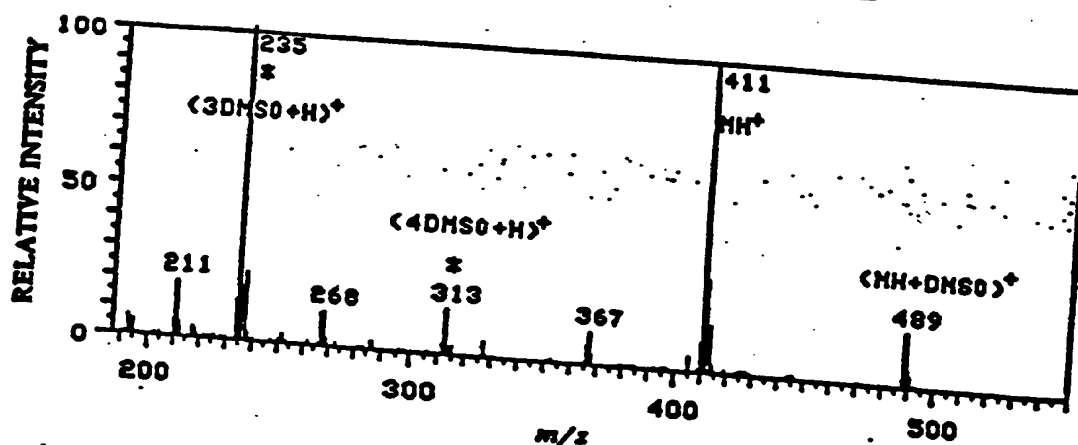


Figure 4: Mass Spectrum of Ceftibuten (Lot 4X804)

6. Infrared Spectrum

The characteristic bands are assigned as shown below.

| Band frequency (cm^{-1}) | Assignment |
|--|---|
| 3582 | OH stretch of crystallization water |
| 3300-2500 | OH stretch of -COOH |
| 3250 | NH stretch |
| 1771 | C=O stretch of β -lactam and of -COOH on side-chain |
| 1701 | C=O stretch of -COOH on cephem ring |
| 1651, 1624 | C=O stretch of amide I |
| 1545 | NH bending of amide II |
| 1364 | CN stretch of aromatic amine |

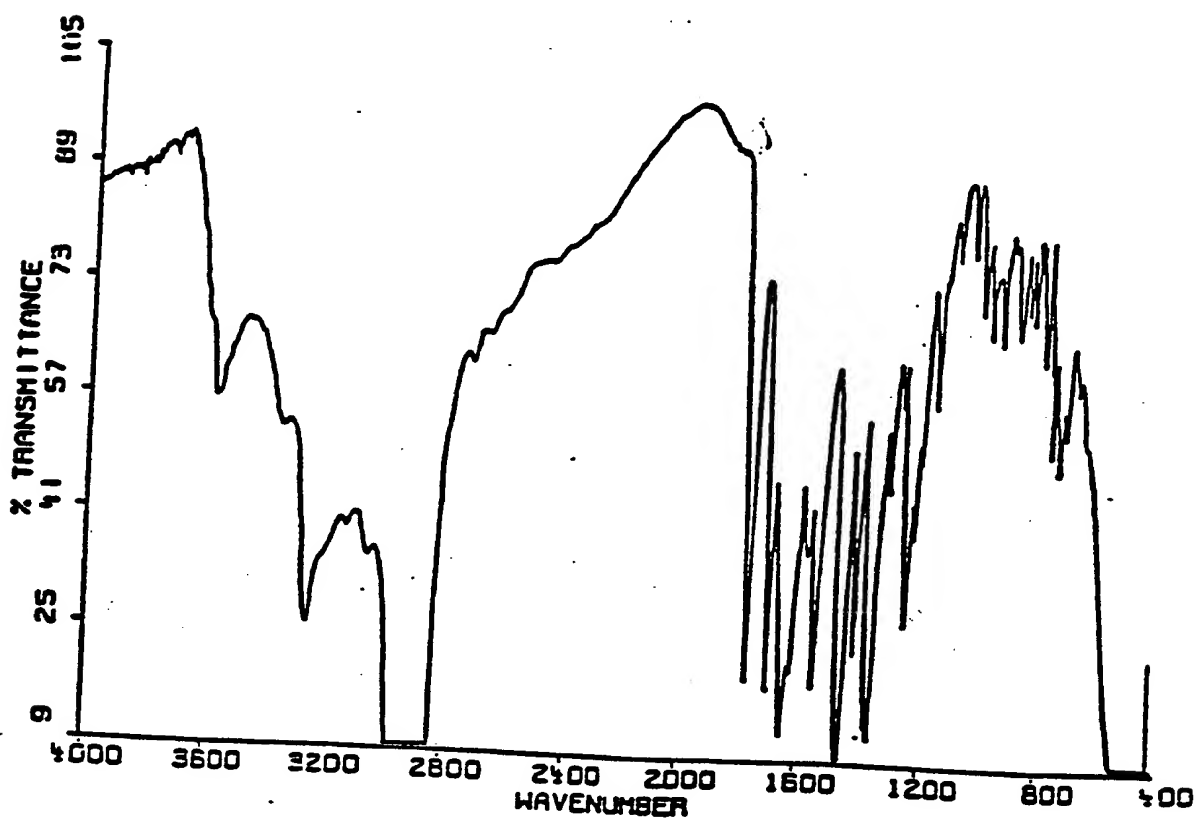


Figure 5: Infrared Spectrum of Ceftibuten (Lot 4X804) in Nujol (Approximate concentration: 1 mg/drop)

7. Ultraviolet Spectrum

Figure 6 shows the ultraviolet (UV) spectra of ceftibuten in water, methanol, and anhydrous ethanol. The absorption band around 262 nm is characteristic of the cephem carboxylic acid structure and the 2-aminothiazole ring.

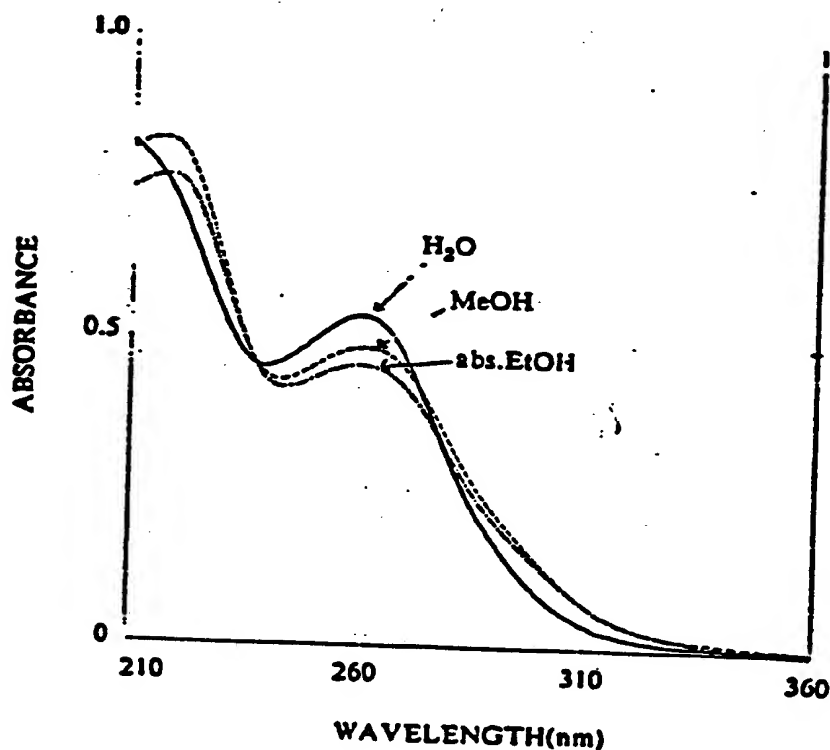


Figure 6: Ultraviolet Spectra of Ceftibuten (Lot 4X804) in Water, Methanol, and Anhydrous Ethanol (20 μ g/ml)

8. Absolute Configuration

The absolute configuration of ceftibuten is R,R at the chiral carbons C₆ and C₇. It was not possible to prove this by single crystal X-ray structure methods on ceftibuten directly, because 12 different attempts to obtain ceftibuten single crystals suitable for single crystal structure determinations were unsuccessful. Ceftibuten's lack of sufficient solubility in some solvents or its fairly rapid conversion to the trans isomer when in solution were the major difficulties encountered in attempts to obtain suitable single crystals of ceftibuten. Recrystallization from dimethylacetamide, dimethylsulfoxide, or N-methylpynolidine with the addition of either acetonitrile, acetonitrile/water, water, or dimethoxyethane/water and various warming/cooling cycles failed to produce crystals of adequate purity. However, single crystal structure analysis of the ceftibuten precursor (3-Norcephem Diester), and the synthesis route provide a solid basis for this conclusion.

Attached is a report^{*} by Tomohiro Sato on the single crystal structure determination of the ceftibuten 3-norcephem diester. This work proves that the hydrogens on the chiral carbons are cis. The fact that they are R,R rather than S,S is based upon the fact that the compound is synthesized from a penicillin starting material. The configuration of the penicillin compound is well established as being R,R and nowhere in the synthesis is the ring containing the chiral centers opened. Supportive evidence for the synthesis is contained in the attached publication by Hamashima, et al, "New Methods for the Conversion of Penicillins into 3-Hydroxycephems" (reprinted from Recent Advances in the Chemistry of β -Lactam Antibiotics).

9. Conclusion

Taken collectively, elemental analysis, proton and carbon-13 nuclear magnetic resonance spectroscopy, infrared spectroscopy, mass spectrometry and ultraviolet spectroscopy prove the assigned ceftibuten structure. The absolute configuration is confirmed by single crystal structure analysis of a ceftibuten intermediate and the synthesis.

Structure of a Ceftibuten Ester

by TOMOHIRO SATO

Shionogi Research Laboratories, Shionogi & Co. Ltd.

Fukushima-ku, Osaka 553, Japan

Abstract. Diphenylmethyl (6*R*,7*R*)-7-[(*E*)-2-(2-benzyloxycarbonylamino-4-thiazolyl)-4-(3-methyl-2-butenoyloxycarbonyl)-2-butenoylamino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate *n*-butyl acetate solvate, $C_{41}H_{38}N_4O_8S_2 \cdot C_6H_{12}O_2$, $M_r = 895.05$, orthorhombic, $P2_12_12$, $a = 16.948(2)$, $b = 19.434(2)$, $c = 14.246(1) \text{ \AA}$, $V = 4692.2(8) \text{ \AA}^3$, $Z = 4$, $D_x = 1.267 \text{ Mg m}^{-3}$, Cu $K\alpha$ radiation, $\lambda = 1.54178 \text{ \AA}$, $\mu = 1.50 \text{ mm}^{-1}$, $F(000) = 1888$, room temperature, $R = 0.060$ for 3570 observed reflections. The molecule has a standard cephem nucleus associated with a 7-substituent having a CC double bond in the *E* configuration. The present study, together with other lines of evidence, has established the stereochemistry of ceftibuten.

Introduction. Ceftibuten (I), previously coded as 7432-S, is a new orally absorbable cephalosporin (Hamashima *et al.*, 1987). Its 3-unsubstituted cephem nucleus is prepared by the Shionogi ring-expansion process starting from penicillin G (Hamashima *et al.*, 1977; Yoshioka, 1987). Since many attempts failed to obtain ceftibuten crystals suitable for X-ray crystallography, we have undertaken the X-ray structure determination of the synthetic precursor (II).

(Scheme)

Experimental. Repeated (four times) recrystallization of a pilot plant product (81.1% of the *E* isomer and 18.4% of the *Z* isomer by HPLC analysis)

from a 1:3:4 mixture of dichloromethan, ethyl acetate and methanol gave an essentially pure *E* isomer (*E* : *Z* = 98.79 : 0.51).

Colorless and rod-like crystals grown from *n*-butyl acetate, D_m not measured. Crystal dimensions: $0.30 \times 0.30 \times 0.40$ mm, Rigaku AFC-5 diffractometer, graphite-monochromated Cu $K\alpha$ radiation. Lattice parameters from 24 reflections ($40 < 2\theta < 55^\circ$). $\omega/2\theta$ scan, $2\theta \leq 130^\circ$, $0 \leq h \leq 19$, $0 \leq k \leq 22$, $0 \leq l \leq 16$, three standard reflections: no variation. 4438 independent reflections measured, 3570 with $I \geq 2\sigma(I)$ considered observed. No absorption correction. Structure solved by direct methods, most of the hydrogens of the cephem ester identified in a difference Fourier map and the remaining hydrogens including those of the solvent molecule calculated using standard geometries. These hydrogens included in the calculation but their parameters not refined. Block-diagonal least squares refinement, anisotropic thermal parameters for non-H atoms, isotropic type-I extinction correction (Becker & Coppens, 1974) with $g = 0.23(1) \times 10^{-4}$, $\sum w(\Delta F)^2$ minimized, $w = 1$, $R = 0.060$, $wR = 0.054$, final $|\text{shift}/\sigma|_{\text{max}} < 0.2$, $-0.44 \leq \Delta\rho \leq 0.44 \text{ e}\text{\AA}^{-3}$. The final atomic parameters are given in Table 1.* Bond distances and angles are listed in Table 2.

All crystallographic calculations were made on a VAX3100 workstation using the program system XTAL2.6 (Hall & Stewart, 1989) with the scattering factors as included in the program.

Discussion. A perspective view of the molecule is shown in Fig. 1.

The molecule has a standard cephem nucleus. The ring torsion angles about the N(1)-C(2), C(2)-C(3), C(3)-C(4), C(4)-S(5), S(5)-C(6) and C(6)-N(1) bonds are $12.7(8)$, $4.3(9)$, $17.1(8)$, $-42.5(5)$, $56.0(4)$ and $-48.3(6)^\circ$, re-

spectively, while the value of $16.1(7)^{\circ}$ is found with the torsion angle S(5)-C(6)-C(7)-N(13). These angles are well compared with those found with other cephalosporins, *e.g.* ceftizoxime (Miyamae, Koda & Morimoto, 1986). Although the present X-ray analysis does not exclude the possibility of the absolute configuration being opposite, the chemical process used for the production of ceftibuten retains the (5*R*, 6*R*) configuration of penicillin G (Hamashima *et al.*, 1977; Yoshioka, 1987). and, therefore, the configurations at C(6) and C(7) are both in the *R* with the present molecule.

The C(16)-C(33) double bond in the 7-substituent has an *E* configuration, the torsion angle C(14)-C(16)-C(33)-C(34) being $-179.0(6)^{\circ}$. The *E* isomer of ceftibuten can be transformed on treatment with acid into *Z*, which is eight times more active than the other (Hamashima *et al.*, 1987).

The packing scheme in the crystal is shown in Fig. 2. The crystal structure contains *n*-butyl acetate (III), which shows no specific interactions with the ceftibuten ester.

Acknowledgement. The authors thank Dr. F. Takami and Mr. A. Okuyama of our Production Department for preparing the crystals used in this study.

*Lists of hydrogen atom parameters, anisotropic thermal parameters and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP XXXXX (15 pp.) Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

- BECKER, P.J. & COPPENS, P., (1974). *Acta Cryst.*, A30, 148-153.
- HALL, S.R. & STEWART, J.M. (1989). Eds. *XTAL2.6 User's Manual*.
Univs. of Western Australia, Australia, and Maryland, USA.
- HAMASHIMA, Y., ISHIKURA, K., ISHITOBI, H., ITANI, H., KUBOTA, T.,
MINAMI, K., MURAKAMI, M., NAGATA, W., NARISADA, M., NISHI-
TANI, Y., OKADA, T., ONOUE, H., SATOH, H., SENDO, Y., TSUJI,
T. & YOSHIOKA, M. (1977). in *Recent Advances in the Chemistry of*
 β -Lactam Antibiotics, edited by J. Elks, pp. 243-251. London: Royal
Society of Chemistry.
- HAMASHIMA, Y., KUBOTA, T., MINAMI, K., ISHIKURA, K., KONOIKE,
T., YOSHIOKA, M., YOSHIDA, T., NAKASHIMIZU, H. & MOTOKAWA,
K., (1987). *J. Antibiot.*, 40, 1468-1470.
- MIYAMAE, A., KODA, K. & MORIMOTO, Y., (1986). *Chem. Pharm. Bull.*,
34, 3539-3548.
- MOTHERWELL, W.D.S. & CLEGG, W. (1978). *PLUTO. Program for plot-*
ting molecular and crystal structures. Univ. of Cambridge.
- YOSHIOKA, M., (1987). *Pure & Appl. Chem.*, 59, 1041-1046.

Table 1. Fractional atomic coordinates and equivalent isotropic thermal parameters (\AA^2)

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

| | <i>x</i> | <i>y</i> | <i>z</i> | <i>U</i> _{eq} |
|-------|------------|------------|-----------|------------------------|
| N(1) | 0.4476(3) | 0.6090(2) | 1.0084(3) | 0.046(3) |
| C(2) | 0.4859(3) | 0.6057(3) | 1.0959(4) | 0.046(3) |
| C(3) | 0.4521(4) | 0.5733(3) | 1.1682(4) | 0.053(3) |
| C(4) | 0.3758(4) | 0.5339(3) | 1.1653(4) | 0.057(4) |
| S(5) | 0.34187(9) | 0.50994(9) | 1.0490(1) | 0.0555(9) |
| C(6) | 0.3649(3) | 0.5908(3) | 0.9954(4) | 0.049(3) |
| C(7) | 0.3817(3) | 0.5886(3) | 0.8876(4) | 0.050(3) |
| C(8) | 0.4690(3) | 0.5941(3) | 0.9180(4) | 0.045(3) |
| O(9) | 0.5316(2) | 0.5872(2) | 0.8800(3) | 0.059(3) |
| C(10) | 0.5607(3) | 0.6449(3) | 1.1098(4) | 0.049(3) |
| O(11) | 0.6041(3) | 0.6379(2) | 1.1754(3) | 0.061(3) |
| O(12) | 0.5706(2) | 0.6903(2) | 1.0406(3) | 0.058(2) |
| N(13) | 0.3600(3) | 0.5312(2) | 0.8323(3) | 0.050(3) |
| C(14) | 0.2957(3) | 0.5347(3) | 0.7762(4) | 0.051(3) |
| O(15) | 0.2526(3) | 0.5852(3) | 0.7765(4) | 0.079(3) |
| C(16) | 0.2796(3) | 0.4739(3) | 0.7144(4) | 0.053(3) |
| C(17) | 0.3439(3) | 0.4233(3) | 0.6959(4) | 0.047(3) |
| N(18) | 0.4158(3) | 0.4475(2) | 0.6658(3) | 0.047(3) |
| C(19) | 0.4643(3) | 0.3973(3) | 0.6514(4) | 0.048(3) |
| S(20) | 0.4280(1) | 0.31632(8) | 0.6738(1) | 0.061(1) |
| C(21) | 0.3395(4) | 0.3543(3) | 0.7049(5) | 0.059(4) |

| | | | | |
|-------|-----------|-----------|-----------|----------|
| N(22) | 0.5411(3) | 0.4104(2) | 0.6236(4) | 0.055(3) |
| C(23) | 0.5928(4) | 0.3598(3) | 0.5966(5) | 0.063(4) |
| O(24) | 0.5779(3) | 0.2998(2) | 0.5964(4) | 0.083(3) |
| O(25) | 0.6607(3) | 0.3895(2) | 0.5729(4) | 0.080(3) |
| C(26) | 0.7254(4) | 0.3428(4) | 0.5489(7) | 0.094(6) |
| C(27) | 0.7334(4) | 0.3351(4) | 0.4455(6) | 0.085(5) |
| C(28) | 0.6837(5) | 0.2961(4) | 0.3942(7) | 0.100(6) |
| C(29) | 0.6927(6) | 0.2882(5) | 0.2982(7) | 0.120(8) |
| C(30) | 0.7524(7) | 0.3201(5) | 0.2544(7) | 0.133(8) |
| C(31) | 0.8040(6) | 0.3601(6) | 0.3074(8) | 0.152(9) |
| C(32) | 0.7946(5) | 0.3680(5) | 0.4001(8) | 0.114(7) |
| C(33) | 0.2070(4) | 0.4675(4) | 0.6795(5) | 0.064(4) |
| C(34) | 0.1777(4) | 0.4109(4) | 0.6182(5) | 0.072(5) |
| C(35) | 0.1243(4) | 0.4357(4) | 0.5412(5) | 0.067(4) |
| O(36) | 0.1068(3) | 0.4949(3) | 0.5265(3) | 0.092(4) |
| O(37) | 0.0990(3) | 0.3832(3) | 0.4900(3) | 0.078(3) |
| C(38) | 0.0488(4) | 0.3986(5) | 0.4084(5) | 0.089(5) |
| C(39) | 0.0948(4) | 0.4312(4) | 0.3301(5) | 0.075(5) |
| C(40) | 0.1435(4) | 0.3989(4) | 0.2747(5) | 0.072(5) |
| C(41) | 0.1885(5) | 0.4351(4) | 0.1974(6) | 0.095(6) |
| C(42) | 0.1608(7) | 0.3249(5) | 0.2843(8) | 0.142(9) |
| C(43) | 0.6349(4) | 0.7395(3) | 1.0514(5) | 0.058(4) |
| C(44) | 0.7120(4) | 0.7109(3) | 1.0147(5) | 0.057(4) |
| C(45) | 0.7172(4) | 0.6581(4) | 0.9507(5) | 0.077(5) |
| C(46) | 0.7891(5) | 0.6360(5) | 0.9174(6) | 0.095(6) |
| C(47) | 0.8566(4) | 0.6665(4) | 0.9487(7) | 0.096(6) |

| | | | | |
|-------|-----------|-----------|-----------|----------|
| C(48) | 0.8534(4) | 0.7185(4) | 1.0114(7) | 0.100(6) |
| C(49) | 0.7816(4) | 0.7403(3) | 1.0463(6) | 0.080(5) |
| C(50) | 0.6084(4) | 0.8027(3) | 0.9984(5) | 0.067(4) |
| C(51) | 0.5674(4) | 0.7967(4) | 0.9148(6) | 0.085(5) |
| C(52) | 0.5426(5) | 0.8526(5) | 0.8660(7) | 0.123(8) |
| C(53) | 0.5594(6) | 0.9169(6) | 0.8965(9) | 0.151(9) |
| C(54) | 0.6028(7) | 0.9252(4) | 0.9756(9) | 0.141(9) |
| C(55) | 0.6281(5) | 0.8670(4) | 1.0309(7) | 0.105(7) |
| C(56) | 0.6675(9) | 0.5372(7) | 0.4242(8) | 0.18(1) |
| C(57) | 0.6136(5) | 0.609(1) | 0.4133(6) | 0.25(2) |
| O(58) | 0.5498(8) | 0.5648(8) | 0.3889(9) | 0.33(2) |
| O(59) | 0.6168(9) | 0.6577(7) | 0.4137(8) | 0.33(2) |
| C(60) | 0.5589(8) | 0.711(1) | 0.398(1) | 0.31(2) |
| C(61) | 0.5743(8) | 0.7736(7) | 0.361(1) | 0.22(1) |
| C(62) | 0.512(1) | 0.8062(7) | 0.308(2) | 0.31(2) |
| C(63) | 0.5463(7) | 0.8716(9) | 0.298(1) | 0.24(2) |

Table 2. Bond distances (Å) and angles (°)

| | | | |
|-------------|----------|-------------|----------|
| N(1)-C(2) | 1.407(7) | N(1)-C(6) | 1.457(7) |
| N(1)-C(8) | 1.369(7) | C(2)-C(3) | 1.336(8) |
| C(2)-C(10) | 1.492(8) | C(3)-C(4) | 1.503(9) |
| C(4)-S(5) | 1.815(6) | S(5)-C(6) | 1.791(6) |
| C(6)-C(7) | 1.563(8) | C(7)-C(8) | 1.544(8) |
| C(7)-N(13) | 1.415(8) | C(8)-O(9) | 1.199(7) |
| C(10)-O(11) | 1.198(7) | C(10)-O(12) | 1.334(7) |
| O(12)-C(43) | 1.457(7) | N(13)-C(14) | 1.353(7) |
| C(14)-O(15) | 1.223(8) | C(14)-C(16) | 1.499(9) |
| C(16)-C(17) | 1.490(8) | C(16)-C(33) | 1.333(8) |
| C(17)-N(18) | 1.376(7) | C(17)-C(21) | 1.349(9) |
| N(18)-C(19) | 1.292(7) | C(19)-S(20) | 1.719(6) |
| C(19)-N(22) | 1.384(7) | S(20)-C(21) | 1.729(7) |
| N(22)-C(23) | 1.373(8) | C(23)-O(24) | 1.193(8) |
| C(23)-O(25) | 1.331(8) | O(25)-C(26) | 1.463(9) |
| C(26)-C(27) | 1.49(1) | C(27)-C(28) | 1.35(1) |
| C(27)-C(32) | 1.38(1) | C(28)-C(29) | 1.38(1) |
| C(29)-C(30) | 1.34(1) | C(30)-C(31) | 1.39(2) |
| C(31)-C(32) | 1.34(2) | C(33)-C(34) | 1.49(1) |
| C(34)-C(35) | 1.50(1) | C(35)-O(36) | 1.206(9) |
| C(35)-O(37) | 1.327(9) | O(37)-C(38) | 1.471(8) |
| C(38)-C(39) | 1.50(1) | C(39)-C(40) | 1.30(1) |
| C(40)-C(41) | 1.51(1) | C(40)-C(42) | 1.47(1) |
| C(43)-C(44) | 1.512(9) | C(43)-C(50) | 1.510(9) |

| | | | |
|-------------------|----------|-------------------|----------|
| C(44)-C(45) | 1.38(1) | C(44)-C(49) | 1.387(9) |
| C(45)-C(46) | 1.38(1) | C(46)-C(47) | 1.36(1) |
| C(47)-C(48) | 1.35(1) | C(48)-C(49) | 1.38(1) |
| C(50)-C(51) | 1.38(1) | C(50)-C(55) | 1.37(1) |
| C(51)-C(52) | 1.36(1) | C(52)-C(53) | 1.35(1) |
| C(53)-C(54) | 1.36(2) | C(54)-C(55) | 1.44(1) |
| C(56)-C(57) | 1.68(2) | C(57)-O(58) | 1.43(2) |
| C(57)-O(59) | .95(3) | O(59)-C(60) | 1.45(2) |
| C(60)-C(61) | 1.35(3) | C(61)-C(62) | 1.44(2) |
| C(62)-C(63) | 1.40(2) | | |
| C(2)-N(1)-C(6) | 123.0(4) | C(2)-N(1)-C(8) | 134.6(5) |
| C(6)-N(1)-C(8) | 94.8(4) | N(1)-C(2)-C(3) | 120.5(5) |
| N(1)-C(2)-C(10) | 119.1(5) | C(3)-C(2)-C(10) | 120.2(5) |
| C(2)-C(3)-C(4) | 126.0(5) | C(3)-C(4)-S(5) | 115.4(4) |
| C(4)-S(5)-C(6) | 95.4(3) | N(1)-C(6)-S(5) | 111.6(4) |
| N(1)-C(6)-C(7) | 87.5(4) | S(5)-C(6)-C(7) | 115.8(4) |
| C(6)-C(7)-C(8) | 84.1(4) | C(6)-C(7)-N(13) | 121.4(5) |
| C(8)-C(7)-N(13) | 117.4(5) | N(1)-C(8)-C(7) | 91.5(4) |
| N(1)-C(8)-O(9) | 133.0(5) | C(7)-C(8)-O(9) | 135.5(5) |
| C(2)-C(10)-O(11) | 124.6(5) | C(2)-C(10)-O(12) | 110.3(5) |
| O(11)-C(10)-O(12) | 125.1(5) | C(10)-O(12)-C(43) | 116.7(5) |
| C(7)-N(13)-C(14) | 119.9(5) | N(13)-C(14)-O(15) | 121.3(6) |
| N(13)-C(14)-C(16) | 116.9(5) | O(15)-C(14)-C(16) | 121.7(5) |
| C(14)-C(16)-C(17) | 119.4(5) | C(14)-C(16)-C(33) | 117.4(5) |
| C(17)-C(16)-C(33) | 123.2(6) | C(16)-C(17)-N(18) | 118.5(5) |
| C(16)-C(17)-C(21) | 126.8(5) | N(18)-C(17)-C(21) | 114.7(5) |

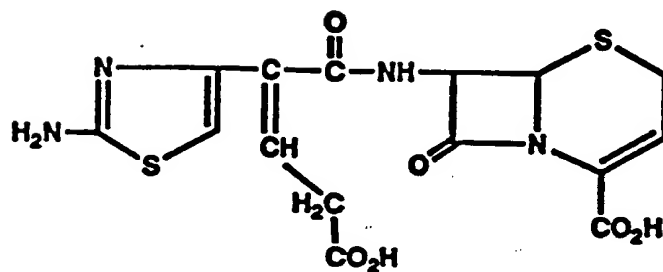
| | | | |
|-------------------|----------|-------------------|----------|
| C(17)-N(18)-C(19) | 110.8(5) | N(18)-C(19)-S(20) | 115.8(4) |
| N(18)-C(19)-N(22) | 120.3(5) | S(20)-C(19)-N(22) | 123.9(4) |
| C(19)-S(20)-C(21) | 88.1(3) | C(17)-C(21)-S(20) | 110.6(5) |
| C(19)-N(22)-C(23) | 123.3(5) | N(22)-C(23)-O(24) | 124.4(6) |
| N(22)-C(23)-O(25) | 108.2(5) | O(24)-C(23)-O(25) | 127.4(6) |
| C(23)-O(25)-C(26) | 115.9(5) | O(25)-C(26)-C(27) | 111.3(6) |
| C(26)-C(27)-C(28) | 122.4(7) | C(26)-C(27)-C(32) | 119.1(7) |
| C(28)-C(27)-C(32) | 118.4(9) | C(27)-C(28)-C(29) | 121.9(8) |
| C(28)-C(29)-C(30) | 119.5(9) | C(29)-C(30)-C(31) | 118.6(9) |
| C(30)-C(31)-C(32) | 122(1) | C(27)-C(32)-C(31) | 119.9(9) |
| C(16)-C(33)-C(34) | 126.5(6) | C(33)-C(34)-C(35) | 113.0(6) |
| C(34)-C(35)-O(36) | 125.6(6) | C(34)-C(35)-O(37) | 110.4(6) |
| O(36)-C(35)-O(37) | 124.0(6) | C(35)-O(37)-C(38) | 117.7(6) |
| O(37)-C(38)-C(39) | 111.9(6) | C(38)-C(39)-C(40) | 125.1(7) |
| C(39)-C(40)-C(41) | 122.4(7) | C(39)-C(40)-C(42) | 122.6(8) |
| C(41)-C(40)-C(42) | 114.9(7) | O(12)-C(43)-C(44) | 111.6(5) |
| O(12)-C(43)-C(50) | 104.9(5) | C(44)-C(43)-C(50) | 112.5(5) |
| C(43)-C(44)-C(45) | 124.0(6) | C(43)-C(44)-C(49) | 118.1(6) |
| C(45)-C(44)-C(49) | 117.9(6) | C(44)-C(45)-C(46) | 121.2(7) |
| C(45)-C(46)-C(47) | 119.6(8) | C(46)-C(47)-C(48) | 120.5(7) |
| C(47)-C(48)-C(49) | 120.3(7) | C(44)-C(49)-C(48) | 120.4(7) |
| C(43)-C(50)-C(51) | 120.7(6) | C(43)-C(50)-C(55) | 120.0(7) |
| C(51)-C(50)-C(55) | 119.2(7) | C(50)-C(51)-C(52) | 121.9(8) |
| C(51)-C(52)-C(53) | 120.7(9) | C(52)-C(53)-C(54) | 119(1) |
| C(53)-C(54)-C(55) | 121.4(9) | C(50)-C(55)-C(54) | 117.2(9) |
| C(56)-C(57)-O(58) | 86(1) | C(56)-C(57)-O(59) | 143(1) |

| | | | |
|--------------------------|---------------|--------------------------|---------------|
| O(58)-C(57)-O(59) | 130(1) | C(57)-O(59)-C(60) | 133(1) |
| O(59)-C(60)-C(61) | 125(1) | C(60)-C(61)-C(62) | 117(1) |
| C(61)-C(62)-C(63) | 99(1) | | |

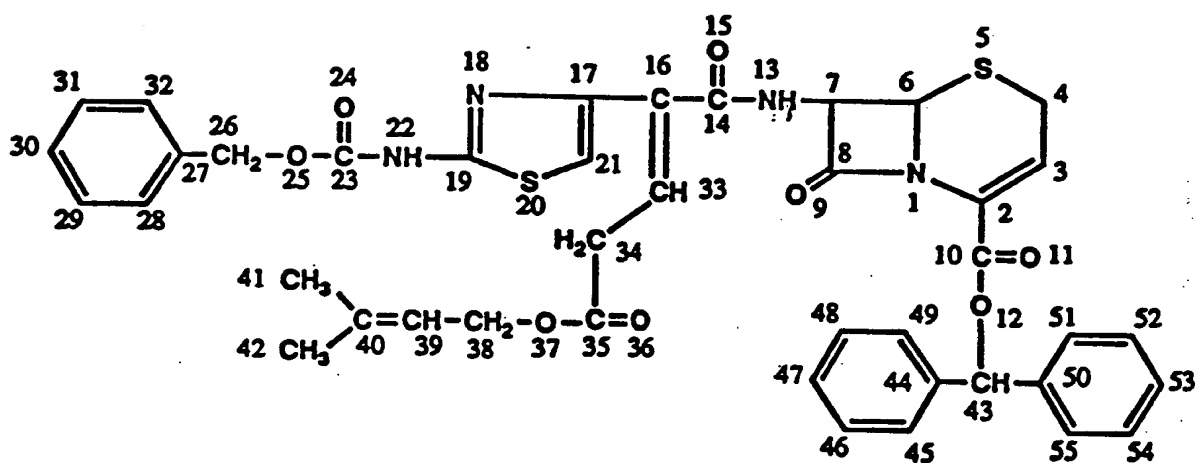
Figure captions

Fig. 1. A perspective view of the cestibuten ester, prepared with *PLUTO* (Motherwell & Clegg, 1978).

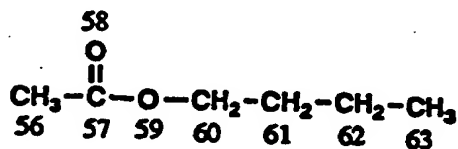
Fig. 2. A [001]-projection of the unit cell, prepared with *PLUTO* (Motherwell & Clegg, 1978).



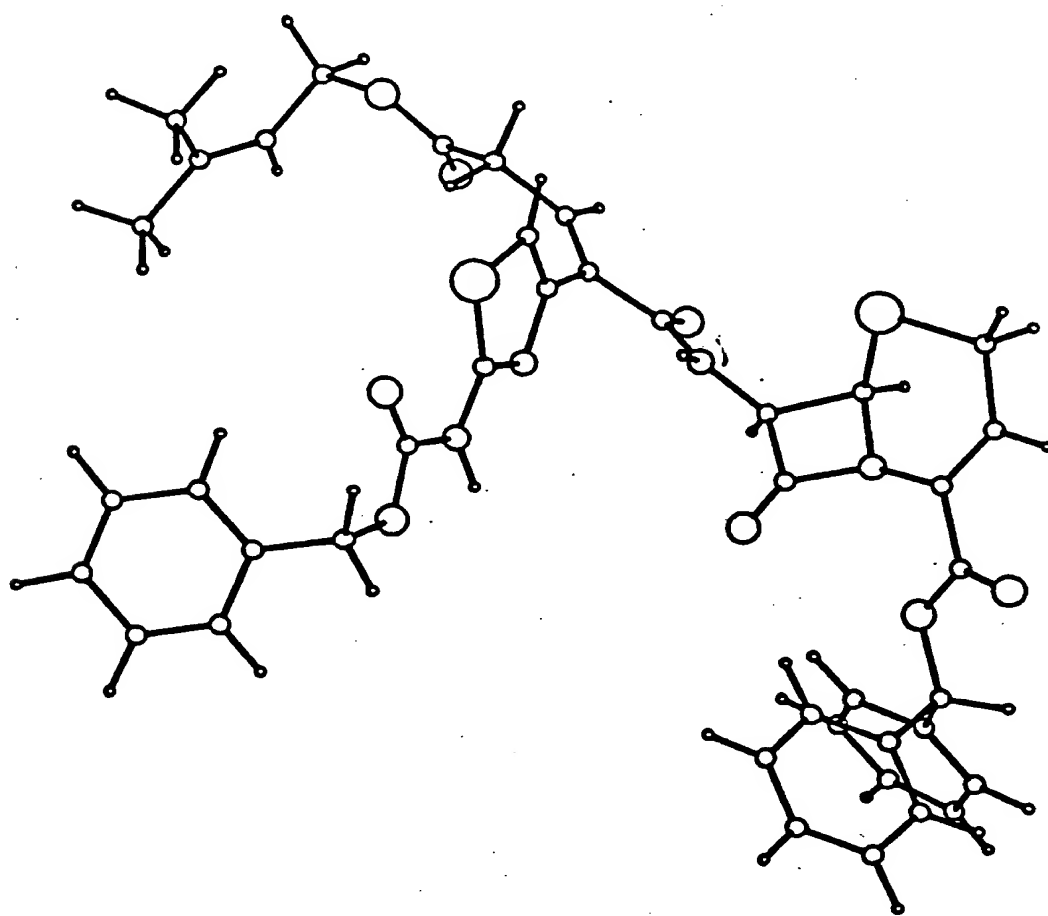
(I)

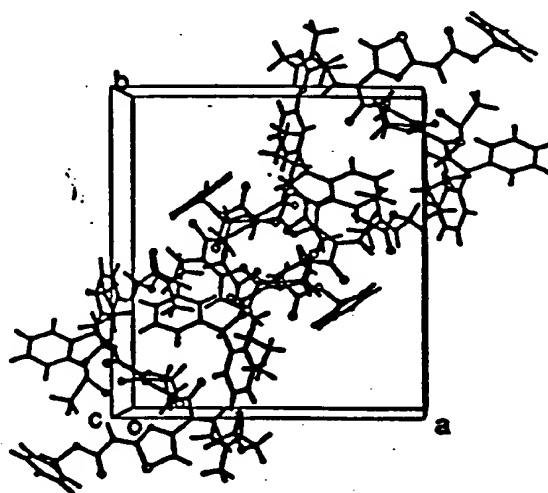
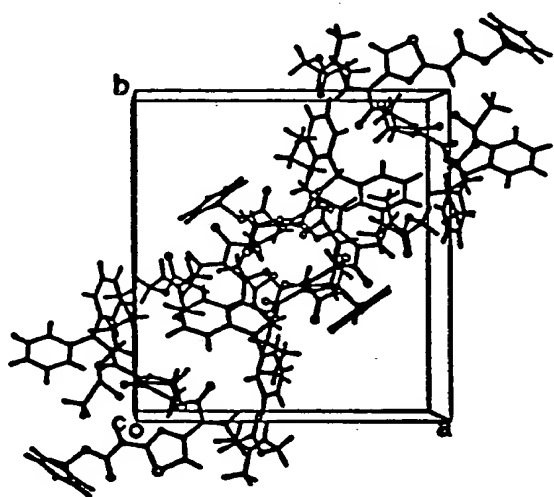


(II)



(III)





United States Patent [19]

Hamashima

[11] Patent Number: 4,634,697

[45] Date of Patent: Jan. 6, 1987

[54] CARBOXYALKENAMIDOCEPHALOSPORINS

[75] Inventor: Yoshio Hamashima, Kyoto, Japan

[73] Assignee: Shionogi & Co., Ltd., Osaka, Japan

[21] Appl. No.: 711,017

[22] Filed: Mar. 12, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 656,731, Oct. 1, 1984, abandoned.

[30] Foreign Application Priority Data

Oct. 4, 1983 [JP] Japan 58-186601

Feb. 3, 1984 [JP] Japan 59-18563

May 18, 1984 [JP] Japan 59-100890

[51] Int. Cl.⁴ A61K 31/545; C07D 501/22; C07D 501/24

[52] U.S. Cl. 514/202; 514/206; 514/207; 514/203; 514/204; 540/215; 540/222; 540/227; 540/228

[58] Field of Search 544/22, 16, 25, 27, 544/28; 514/202, 203, 204, 206, 207

[56] References Cited

U.S. PATENT DOCUMENTS

3,994,888 11/1976 Kukolja 260/243 C
 4,014,869 3/1977 Gregory 544/16
 4,416,980 11/1983 Boberg 514/210
 4,500,716 2/1985 Kinast 544/28

FOREIGN PATENT DOCUMENTS

2076301 12/1981 United Kingdom 544/22

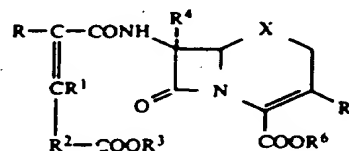
Primary Examiner—Sidney Marantz

Assistant Examiner—Robert Benson

Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

An antibacterial 7beta-(carboxyalkenoyl)amino-3-cephem-4-carboxylic acid represented by the following formula:



(wherein

R is aryl or a heterocyclic group;

R¹ is hydrogen or halogen;R² is a single bond, alkylene, or thiaalkylene;R³ is a hydrogen atom or carboxy modifying group;R⁴ is hydrogen or methoxy;R⁵ is hydrogen or a 3-substituent of cephalosporins;R⁶ is a hydrogen atom or carboxy modifying group; and

X is oxygen, sulfur, or sulfinyl)

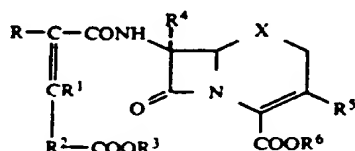
a pharmaceutical composition containing the same, and a method for treating a bacterial infection with the same.

18 Claims, No Drawings

CARBOXYALKENAMIDOCEPHALOSPORINS

This application is a continuation in part of application Ser. No. 656,731, filed Oct. 1, 1984 (now abandoned).

This invention relates to antibacterial 7beta-(carboxyalkenylamino)-3-cephem-4-carboxylic acids represented by the following formula:



(wherein

R is aryl or a heterocyclic group;

R¹ is hydrogen or halogen;

R² is a single bond, alkylene, or thiaalkylene;

R³ is a hydrogen atom or carboxy modifying group;

R⁴ is hydrogen or methoxy;

R⁵ is hydrogen or a 3-substituent of cephalosporins;

R⁶ is a hydrogen atom or carboxy modifying group; and

X is oxygen, sulfur, or sulfinyl)

The following explains the variable groups of the formula (I):

R as aryl is optionally substituted phenyl. R as a heterocyclic group is an optionally substituted 5 or 6 membered monocyclic ring group containing 1 to 4 hetero atoms selected from oxygen, nitrogen, and sulfur. Representative rings are pyrrol, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, thia-triazolyl, pyridyl, pyrimidyl, pyrazinyl, triazinyl, and the like. Here, the said substituents include, among other conventional ones, alkyl, substituted alkyl, carboxy, protected carboxy, amino, protected amino, hydroxy, protected hydroxy, halogen, sulfamoyl, and the like. Among the protecting groups in the protected amino, preferred are 7 to 20C optionally substituted aralkyl (e.g., benzyl, benzhydryl, trityl, methoxybenzyl, dimethoxybenzyl, nitrobenzyl, methylbenzyl, dimethylbenzyl), 1 to 8C optionally substituted alkyl (e.g., trichloromethyl, trichloroethyl, trifluoromethyl, tetrahydropyrany), substituted phenylthio 1 to 8C substituted alkylidene, 7 to 14C substituted aralkylidene, 5 to 8C substituted cycloalkylidene, acyl [e.g., 1 to 8C optionally substituted alkanoyl (e.g., formyl, acetyl, chloroacetyl, trifluoroacetyl), 2 to 12C optionally substituted lower alkoxy carbonyl (in which the alkyl part is methyl, ethyl, propyl, cyclopropylethyl, isopropyl, butyl, pentyl, hexyl, trichloroethyl, pyridylmethyl, cyclopentyl, cyclohexyl, quinolylmethyl, or the like), 8 to 15C optionally substituted aralkoxy carbonyl (in which the aralkyl part is benzyl, diphenylmethyl, nitrobenzyl, or the like), succinyl, phthaloyl, trialkylsilyl, alkoxydialkylsilyl, trialkylstannyl, and the like.

Preferably R is one selected from phenyl, furyl, thienyl, oxazolyl, isoxazolyl, optionally protected aminoisoxazolyl, triazolyl, optionally protected aminothiazolyl, thiadiazolyl, and aminothiadicazolyl. An optionally protected aminothiazolyl is more preferable.

R¹ as halogen is fluorine or chlorine, especially chlorine. Preferably R¹ is hydrogen.

The alkylene part in R² is lower alkylene, preferably 1 to 3C alkylene, especially methylene.

R⁵ as a substituent of cephalosporins can be, among others, hydroxy, alkanoyloxy, halogen, alkoxy, alkylthio, alkenylthio, alkyl (e.g., methyl), alkenyl (e.g., vinyl, cyanovinyl, trifluoropropenyl), substituted methyl, or the like which are well known 3-substituents of cephalosporins. Here, the substituent in the said substituted methyl can be pyridinio, substituted pyridinio, halogen, hydroxy, alkoxy, acyloxy (e.g., acetoxy, carbamoyloxy), alkylthio, haloalkylthio, cyanoalkylthio, heterocyclic thio (e.g., triazolylthio, methyltetrazolylthio, thiadiazolylthio optionally substituted by amino, aminomethyl, alkoxy, or methyl), triazolyl, tetrazolyl, or the like. The said alkyl part is preferably methyl. Preferably R⁵ is hydrogen, vinyl, carbamoyloxymethyl, tetrazolylthiomethyl, or thiadiazolylthiomethyl.

R³ or R⁶ as a carboxy-modifying group is preferably an ester forming group or salt forming atom or group each useful as a carboxy-protecting group or one for a medical derivative.

Preferably X is sulfur.

The said carboxy-protecting group is known in penicillin and cephalosporin fields as it can be introduced and removed without adverse effect on other part of the molecule. Representative are an inorganic salt (e.g., lithium, sodium, potassium, magnesium, calcium, aluminum, or ammonium salt), organic base salt, for example, alkylamine salt (e.g., ethylamine, diethylamine, triethylamine, piperidine, morpholine, N-methylmorpholine salt), aromatic amine salt (e.g., aniline, dimethylaniline salt), aromatic base salt (e.g., pyridine, picoline, lutidine, nicotinamide, quinoline salt), optionally substituted 1 to 8C alkyl ester (e.g., methyl, methoxymethyl, ethoxymethyl, ethyl, methoxyethyl, trichloroethyl, iodoethyl, propyl, isopropyl, ethoxyethyl, methylthioethyl, methanesulfonyl ethyl, methanesulfonylmethyl, butyl, isobutyl, t-butyl, hexyl ester), 7 to 15C aralkyl ester (e.g., benzyl, methylbenzyl, dimethylbenzyl, methoxybenzyl, ethoxybenzyl, nitrobenzyl, aminobenzy, phenethyl, diphenylmethyl, trityl, phenaldehyd, phenacyl, di-t-butyl-hydroxybenzyl ester), 6 to 12C aryl ester (e.g., phenyl, tolyl, diisopropylphenyl, xylyl, trichlorophenyl, indanyl ester), 3 to 12C silyl ester (e.g., trimethylsilyl, t-butyl dimethylsilyl, dimethylmethoxysilyl ester), 3 to 12C stannyl ester (e.g., trimethylstannyl ester), 1 to 12C N-hydroxyamino ester (ester with e.g., acetone oxim, acetophenone oxim, acetaldoxim, N-hydroxysuccinimide, N-hydroxyphthalimide), 2 to 7C alkenyl ester (e.g., vinyl, propenyl, allyl ester), and the like. Anhydrides with carbonic or carboxylic acid, reactive amides, and the like are equivalent carboxy-protecting group. Said protecting part may further be substituted.

Preferably R³ and R⁶ as carboxy protecting groups are hydrogen, sodium, potassium, methyl, t-butyl, phenyl, indanyl, benzyl, cyanobenzy, halobenzy, methylbenzy, nitrobenzy, phenylbenzy, or the like.

The protecting group is absent in objective products. So, its structure has in itself no specific meaning, as far as the group serves well for the protection and thus it can be replaced by a wide variety of equivalent groups.

Especially useful carboxy derivatives are medically available ones including light metal salts and pharmaceutically acceptable esters. The preferred light metals are those forming physiologically acceptable ions and belonging to the 1st to 3rd group, 2nd to 4th periods of the Periodical Table. Lithium, sodium, potassium, mag-

nesium, calcium, aluminum, and the like are preferable. The pharmacological esters show antibacterial potency on administering orally or parenterally and include well known 3 to 12C 1-substituted alkyl esters, for example, alkanoyloxyalkyl esters (e.g., acetoxymethyl, acetoxylethyl, propionyloxyethyl, pivaloyloxymethyl, pivaloyloxyethyl, tetrahydrofuryl, tetrahydropyranyl ester), 3 to 8C alkoxyformyloxyalkyl esters (e.g., ethoxycarbonyloxyethyl ester), 7 to 15C substituted aralkyl esters (e.g., phenacyl, phthalidyl ester), 6 to 12C substituted aryl esters (e.g., phenyl, xylyl, indanyl ester), and 2-alkenyl esters (e.g., allyl, 2-oxo-1,3-dioxolenylmethyl ester).

Both of the geometric isomers at the double bond in the 7-side chain are antibacterials. Among them, those having the R and R¹ in the cis position are more potent antibacterials. The other geometric isomers (trans) are useful also as an intermediate for preparing the corresponding cis isomer.

Some of the representative Compounds (I) of this invention are listed below. These should not be taken as an exhaustive listing of the compounds of this invention.

- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-vinyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoropropenyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-acetoxymethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxymethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methylthiomethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-pyridinioethyl-3-cephem-4-carboxylate,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-triazolylthiomethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-thiadiazolylthiomethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyltetrazolylthiomethyl-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxy-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-chloro-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-fluoroethylthio-3-cephem-4-carboxylic acid,

- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoroethylthio-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-5-carboxy-2-pentenoylamino]-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-6-carboxy-2-hexenoylamino]-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-pentenoylamino]-3-cephem-4-carboxylic acid,
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-4-methyl-2-pentenoylamino]-3-cephem-4-carboxylic acid, and
- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-3-chloro-2-butenoylamino]-3-cephem-4-carboxylic acid.

Some compounds closely related to Compounds (I) are disclosed in Japanese patent publication Kokoku No. 10,996/1967, Kokai No. 57-93982, and Belgian Pat. Nos. 816,408 and 888,389. These are not superior to Compounds (I) in their antibacterial activity, enteral or parenteral absorbability, excretion, or the like characteristics.

Compounds (I) are antibacterials against aerobic Gram-positive bacteria (e.g., *Bacillus cereus*, *Bacillus subtilis*, *Corynebacterium diphtheriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, enterococci) and Gram-negative bacteria (e.g., *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus morgani*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, *Salmonella paratyphi*, *Salmonella typhi*, *Serratia marcescens*, *Shigella sonnei*, *Yersinia enterocolitica*), including anaerobic bacteria (e.g., *Bacteroides fragilis*, *Clostridium difficile*, *Clostridium perfringens*, *Eubacterium lentum*, *Fusobacterium nucleatum*, *Propionibacterium* spp, peptostreptococci, *Veillonella* spp.).

Especially, high anti-Gram-negative potency, high absorption, excretion, distribution, and the like are remarkable. As a medicine for preventing or treating a bacterial infection, Compound (I) is administered orally, parenterally, or topically at a daily dose of 10 micrograms to 6 grams, if required formulating with conventional additives or coacting substances, e.g., other antibacterials.

They are useful as bacteriocidal, bacteriostatic, disinfecting, or antiperishable agents and useful for treating or preventing human, veterinary, or poultry infections caused by sensitive Gram-positive bacteria or Gram-negative bacteria, including anaerobic bacteria. Further, they are useful as bacterial growth inhibitors on human, animal, plant, or perishable subjects, human or animal growth promoting additives in foodstuff, or as agents for testing sensitivity of bacteria to the antibacterial (I).

Protected compounds (I) are also useful as starting materials for synthesizing other antibacterials (I).

This invention also provides a method for treating or preventing human or veterinary bacterial infections (e.g., abscess, bronchitis, dermatitis, ear infections, empyema, enteritis, gastroenteritis, nasopharyngitis, osteomyelitis, pneumonitis, pneumonia, pustulosis, pyelonephritis, respiratory tract infections, rhinitis, septicemia, tonsillitis, ulceration, urinary tract infections, wound and soft tissue infections) caused by sensitive bacteria by administering an effective amount of Compound (I)

at a typical daily dose of 10 micrograms to 1 gram externally, 0.2 to 5 grams intravenously, or 0.1 to 2 grams orally at an interval of 3 to 12 hours depending on the infecting bacteria and condition of the patient, if required formulating with a conventional additive.

Compound (I) as carboxylic acid or its light metal salt can be injected or infused intravenously, intramuscularly or subcutaneously (as e.g., injection, pellet), or give orally (as oral preparations, e.g., capsule, dry syrup, emulsion, granules, powder, solution, suspension, tablet, troche), if required in admixture with an excipient (e.g., emulsifying agent). A pharmacological ester can be given intravenously, intramuscularly, subcutaneously, orally, externally, or topically (as e.g., ear, nasal, or ocular drug, ointment, inhalant, injection, pap preparation, spray, suppository).

When R is 2-amino-4-thiazolyl, R² is methylene, R¹, R³, R⁴, and R⁶ are hydrogens, and R⁵ is hydrogen, methyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, vinyl, fluoro-propenyl, methoxy, chlorine, fluoroethylthio, or trifluoroethylthio, Compound (I) is absorbed orally as well as subcutaneously. Its pharmaceutically acceptable esters are also absorbed through the digestive organs.

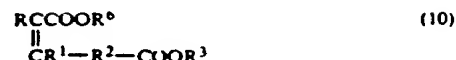
Further, this invention provides an antibacterial pharmaceutical composition containing Compound (I) in various enteral or parenteral dosage forms solely or in admixture with carriers or coacting substances. The compositions may contain 0.01 to 99% of Compound (I) dissolved, dispersed, or suspended in solid or liquid pharmaceutical carriers.

The compositions may be solid preparations (e.g., capsule, dry syrup, granule, pellet, pill, powder, suppository, troche, tablet) or liquid preparations (e.g., dispersion, elixir, emulsion, inhalant, injection, ointment, suspension, syrup, solution from ampoule or vial containing crystals, lyophilized material, or powder). They can be flavored or colored, and capsules, granules, and tablets may be coated. They can be in a unit dosage form.

The carriers are harmless to both the Compound (I) and patients. Representative examples of such carriers are, among others, for solids, binders (e.g., acacia, carboxymethylcellulose, gelatin, glucose, polyvinylpyrrolidone, sodium alginate, sorbitol, starch, syrup, tragacanth), bulking agents (e.g., bentonite, calcium carbonate, calcium phosphate, glycine, kaolin, lactose, polycarboxymethylene, salt, sorbitol, starch, sugar, talc), diluents (e.g., calcium carbonate, kaolin, lactose, starch, sucrose), disintegrators (e.g., agar, carbonates, sodium laurylsulfate, starch), lubricants (e.g., boric acid, cacao oil, magnesium stearate, paraffin, polyethylene glycol, silica, sodium benzoate, stearic acid, talc), and wetting agents (e.g., hydroxypropyl cellulose); for solutions, solvents (e.g., alcohol, buffer, methyl oleate, peanut oil, sesame oil, water), emulsifying agents (e.g., acacia, lecithin, sorbitan monooleate), suspending agents (e.g., aluminum stearate gel, carboxymethyl cellulose, gelatin, glucose, hydrogenated fats, hydroxyethylcellulose, methyl cellulose, sorbitol, sugar syrup), buffers, dispersing agents, and solubilizing agents; and for both, preservatives (e.g., methyl or ethyl p-hydroxybenzoate, sorbic acid), absorption promoters (e.g., glycerin mono- or di-octanoate), antioxidants, aromatic substances, analgesics, edible coloring agents, stabilizing agents, and the like.

All of above pharmaceutical preparations can be prepared in conventional manner.

This invention also provides Carboxyalkenoic acid (10) useful as an intermediate for preparing the said Compound (I),



(wherein R, and R¹ to R⁶ are as defined for Compound (I)).

In the formula above, examples of the preferred R are phenyl, thienyl, aminoisoxazolyl, thiadiazolyl, aminothiadiazolyl, and aminothiazolyl, said amino can be protected with benzyloxycarbonyl, methylbenzyloxycarbonyl, t-butoxycarbonyl, methoxyethoxymethyl, formyl, chloroacetyl, benzylidene, dimethylaminomethylidene, or the like; preferably R¹ is hydrogen; preferably R² is 1 to 3C optionally branched alkylene, especially methylene; and examples of preferably R³ and R⁶ are the same or different groups selected from hydrogen, methyl, ethyl, t-butyl, trichloroethyl, benzyl, methylbenzyl, diphenylmethyl, trityl, and the like.

Compounds of this invention can be synthesized, for example, by the following methods:

(1) Salt Formation

Compound (I) having carboxy or the cephem nucleus at position 4 or in the 7-substituent can form a light metal salt (I) by reacting with a base or by an exchange reaction with the corresponding light metal salt of other carboxylic acid. The procedure can be that conventional in the art, e.g., by neutralizing the free acid (with a base, e.g., light metal hydroxide, carbonate, or hydrogen carbonate) and evaporating the solvent, or by treating with light metal lower carboxylate in a polar organic solvent (e.g., alcohol, ketone, ester) and then adding a sparingly dissolving less polar solvent to separate the salt. The solvent may be removed by filtering.

(2) Deprotection of Carboxy-Protecting Groups Etc.

A protected-carboxy in Compound (I) can conventionally be deprotected, for example, as follows:

(a) A highly reactive ester or anhydride as a carboxy-protecting group can be deprotected by contacting in an aqueous solvent with an acid, base, buffer solution, or ion exchange resin. When its reactivity is insufficient, one can increase it in a conventional manner to deprotect more easily (e.g., by activating of a trichloroethyl ester with metal and acid; p-nitrobenzyl ester with hydrogen and catalyst (e.g., palladium, nickel), dithionate, or metal and acid; and phenacyl ester with irradiation).

(b) An aralkyl ester can be deprotected by a conventional catalytic reduction with hydrogen in the presence of a catalyst (e.g., platinum, palladium, nickel).

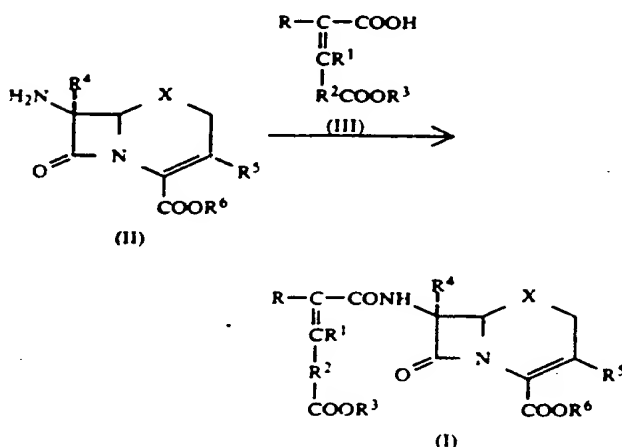
(c) An aralkyl, cyclopropylmethyl, sulfonyl ethyl, or the like ester can be deprotected by solvolysis [with a mineral acid, Lewis acid (e.g., aluminium chloride, tin chloride, titanium tetrachloride), sulfonic acid (e.g., methanesulfonic acid, trifluoromethanesulfonic acid), strong carboxylic acid (trifluoroacetic acid), or the like], if required in the presence of a cation scavenger.

An amino-protecting group in Compound (I) can conventionally be deprotected, for example, as follows: substituted alkyl (e.g., tetrahydropyranyl), aralkyl group (e.g., trityl), alkylidene, aralkylidene, alkanoyl (e.g., formyl), trialkylsilyl, trialkylstannyl, or the like can be deprotected with an aqueous or nonaqueous

acid; an alkoxyformyl (e.g., t-butoxycarbonyl), aralkoxyformyl (e.g., benzyloxycarbonyl, methylbenzyloxycarbonyl), aralkyl (e.g., trityl), or the like can be deprotected with a Lewis acid in the presence of an acid scavenger; haloalkoxycarbonyl (e.g., trichloroethyl, iodoethoxycarbonyl), aralkoxycarbonyl (e.g., benzyloxycarbonyl), or the like can be deprotected by reduction; and phenylthio or acyl (e.g., alkanoyl, succinyl, phthaloyl) can be deprotected with a base.

Deprotection of other protecting groups for hydroxy or the like functional groups in Compound (I) can be carried out according to methods well known in the field of penicillin and cephalosporin chemistry as described in various scientific and patent publications.

(3) Amidation



A conventional reaction of Amine (II) or its reactive derivative with Carboxylic acid (III) or its reactive derivative gives Compound (I) or its derivatives.

The reactive derivative of Amine (II) is that having 7-amino activated by silyl (e.g., trimethylsilyl, methoxydimethylsilyl, t-butyldimethylsilyl), stannyl (e.g., trimethylstannyl), alkylene (as a part of enamino of the amino with e.g., aldehyde, acetone, acetylacetone, acetoacetate, acetoacetonitrile, acetoacetanilide, cyclopentanedione, acetylbutyrolactone), alkylidene (e.g., 1-haloalkylidene, 1-haloaralkylidene, 1-alkoxyalkylidene, 1-alkoxyaralkylidene, 1-alkoxy-1-phenoxyalkylidene, alkylidene, aralkylidene), acid (e.g., mineral acid, carboxylic acid, sulfonic acid as a salt of the amino), easily removable acyl (e.g., alkanoyl), or the like, or that protected at other functions of the molecule.

Free acid (III) is reacted in the presence of a condensing reagent [carbodiimide (e.g., N,N'-diethylcarbodiimide, N,N'-dicyclohexylcarbodiimide), carbonyl compound (e.g., carbonyl diimidazole), isoxazolinium salt, acylamino compound (e.g., 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline), etc.].

The reactive derivative of Carboxylic acid (III) can be an acid anhydride, e.g., symmetric anhydride or mixed anhydride [with mineral acid (e.g., phosphoric acid, sulfuric acid, hydrohalogenic acid, carbonic half ester), organic acid (e.g., alkanic acid, aralkanoic acid, sulfonic acid), intramolecular anhydride (e.g., ketene, isocyanate), etc.], acid halide, reactive ester [enol ester (e.g., vinyl ester, isopropenyl ester), aryl ester (e.g., phenyl ester, halophenyl ester, nitrophenyl ester), heterocyclic ester (e.g., pyridyl ester, benzotriazolylester), an ester with N-hydroxy compound, diacylhydroxyala-

mine ester (e.g. N-hydroxysuccinimide ester, N-hydroxyphthalimide ester), thioester (e.g., aralkyl thiol ester, heterocyclic thiol ester) or the like], or reactive amide [aromatic amide (amide with e.g., imidazole, triazole, 2-ethoxy-1,2-dihydroquinoline), diacylanilide]. The acid scavenger to be used with the said derivative is, for example, inorganic base (e.g., oxide, hydroxide, carbonate, hydrogen carbonate, of alkali metal or alkaline earth metal, etc.), organic base (e.g., tertiary amine, aromatic base), oxirane, (e.g., alkylene oxide, aralkylene oxide), pyridinium salt (e.g., tripyridiniumtriazine trichloride), adsorbent (e.g., Celite), or the like.

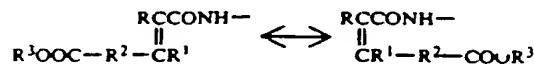
(4) Introduction of 3-Function

Compound (I) having 3-nucleophile substituted-methyl can be prepared by reacting an analog of Compound (I) having a leaving group-substituted methyl at the 3 position on the cephem ring with a heterocyclic thiol, aromatic base, or its reactive derivatives. Here, the leaving group can be, among others, halogen, sulfonyloxy, alkanoyloxy, dihaloalkanoyloxy, trihaloacetoxo, or the like. The said reactive derivative of thiol can be, among others, alkali metal salt, ammonium salt, carboxylate ester, or the like. The reaction can be carried out well in a dry or wet solvent at 0° C. to 60° C. This reaction can be promoted with a dehydrating reagent, phosphoryl chloride compound, rhodanate, or the like.

Compound (I) having 3-acyloxymethyl (e.g., alkanoyloxymethyl, carbamoyloxymethyl) can be made from the corresponding 4-protected carboxy-3-hydroxymethyl-3-cephem derivative by the action of an acylating reagent for introducing the corresponding acyl group.

Compound (I) having no carbon linked to the 3-position can be made from the corresponding 3-hydroxy-3-cephem or its oxo form, for example, by activating the 3-hydroxy (e.g., acylating or halogenating), and then substituting it with a nucleophilic reagent to give a 3-nucleophile substituted compound; a basic or thermal elimination reaction of the corresponding 3-(hydroxy, acyloxy, or halo)cepham compounds or a reduction of 3-(acyloxy or halo)-3-cephem compounds to give a 3-hydrogen-3-cephem compound; or the like conventional 3-modification.

(5) Isomerization at the 7-side chain double bond



The said geometric isomers are interconvertible by isomerization. This reaction is preferably carried out in a protic solvent by the action of acid, base, or light. The acid can be a mineral acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid), carboxylic acid (e.g., formic acid, trifluoroacetic acid), sulfonic acid (e.g., methanesulfonic acid, benzenesulfonic acid), or the like. The base can be inorganic base (e.g., sodium hydroxide, sodium hydrogen carbonate, potassium carbonate), organic base (e.g., triethylamine, potassium t-butoxide), or the like.

Compound (I) wherein R² is 1 to 3C alkylene easily isomerizes under various conditions.

In a typical condition, Compound (I) as free carboxylic acid is dissolved in water at pH 8, acidified to pH 0 to 1, kept at 0° C. to 100° C. for 1 to 10 hours to obtain

an epimeric mixture. Thermally stable isomer is in trans form. Usual separation (e.g., crystallization, precipitation, high precision liquid chromatography, adsorption and elution) gives the geometric isomers in a pure form.

(6) Other Synthetic Methods

(a) Sulfoxide formation—Cephem Compound (I) is conventionally oxidized with an oxidizing reagent (e.g., hydrogen peroxide, percarboxylic acid, iodobenzene dichloride) in an inert solvent at 0° to 60° C. for 0.2 to 5 hours to give the corresponding Cephem-1-oxide (I).

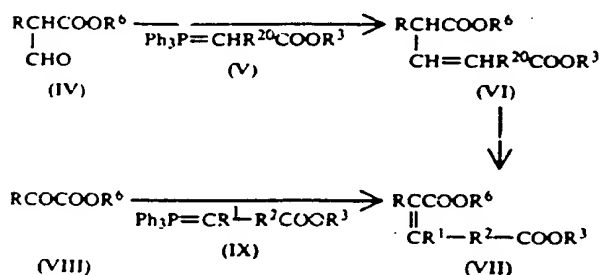
(b) Sulfoxide reduction—Cephem-1-oxide compound (I) is reduced conventionally with a trivalent phosphorus compound, lower valent metal compound hydrogen iodide, or the like in an inert solvent at 0° to 30° C. for 0.1 to 10 hours giving the corresponding Cephem compound (I).

(c) Double bond migration—The 2-double bond of the corresponding 2-cephem compound is conventionally migrated with base at 0° to 80° C. for 1 to 10 hours to give 3-Cephem compound (I).

(d) Ring closure—Compound (I) may be synthesized by a conventional ring closure reaction forming a heterocyclic R group in a manner analogous to those described above under the section of (7) Synthesis of the side chain acids.

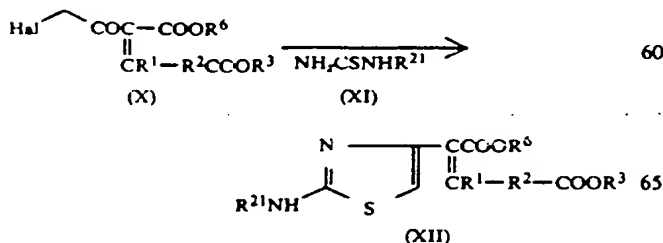
(7) Synthesis of the Side Chain Fragment Acids

The 7-side chain acids are novel compounds prepared by Wittig type reaction of Formylacetate (IV) or its enol or acetal with Alkylidenetriarylphosphorane (V) by heating, e.g., at 30° C. to 120° C. for 1 to 10 hours, to give Nonconjugated ester (VI) the double bond of which migrates to give Conjugate ester (VII):



(wherein R^{20} is alkylene or a single bond) or of Oxalate (V.II) with Alkylidenetriarylphosphorane (IX), e.g., at 30° C. to 120° C. for 1 to 10 hours to give Conjugate ester (VII).

Alternatively, it is produced by a ring closure of Haloacetylcarboxylic acid (X) with optionally N-protected thiourea (XI) in alcohol at 30° C. to 90° C. for 1 to 5 hours giving Amino-thiazole ester (XII):



(wherein R^{21} is hydrogen or amino protecting group) When R^3 and/or R^6 of Conjugated acid (VII) or (XII) is carboxy protecting group, it may be deprotected conventionally by treating with acid, base, Lewis acid and cation scavenger, hydrogen and catalyst, or the like to give the corresponding free acid, preferably in an inert solvent at -60° C. to 100° C. for 1/6 to 10 hours.

Representative synthesis of the side chain carboxylic acids are given under the section of preparations.

(8) Reaction Conditions

The said reactions (1) to (7) can usually be carried out at -60° C. to 120° C., preferably at -20° C. to 80° C. for 10 minutes to 10 hours depending on the type of reaction. These are done in a solvent. Other conventional conditions (e.g., stirring, shaking, inert gas sealing, drying) may be used.

Examples of typical reaction solvents are hydrocarbons (e.g., pentane, hexane, octane, benzene, toluene, xylene), halohydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, dichloroethane, trichloroethane, chlorobenzene), ethers (e.g., diethyl ether, methyl isobutyl ether, dioxane, tetrahydrofuran), ketones (e.g., acetone, methyl ethyl ketone, cyclohexanone), esters (e.g., ethyl acetate, isobutyl acetate, methyl benzoate), nitrohydrocarbons (e.g., nitromethane, nitrobenzene), nitriles (e.g., acetonitrile, benzonitrile), amides (e.g., formamide, acetamide, dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide), sulfoxides (e.g., dimethyl sulfoxide), carboxylic acids (e.g., formic acid, acetic acid, propionic acid), organic bases (e.g., diethylamine, triethylamine, pyridine, picoline, collidine, quinoline), alcohols (e.g., methanol, ethanol, propanol, hexanol, octanol, benzyl alcohol), water, and other industrial solvents and mixtures thereof.

(9) Work Up

The products can be obtained from a reaction mixture by removing contaminants (e.g., solvents, unreacted starting materials, by-products) by a conventional method (e.g., extracting, evaporating, washing, concentrating, precipitating, filtrating, drying), and isolating the product by a usual work up (e.g., adsorbing, eluting, distilling, precipitating, separating, chromatographing), or a combination of said procedures.

(10) Oral Availability

Some compounds (I) having methylene as R^2 are absorbed well through the digestive organs and are available as oral cephalosporins. Especially efficient are those having 2-aminothiazol-4-yl as R, hydrogen as R^3 and R^6 , and hydrogen, vinyl, cyanovinyl, trifluoropropenyl, acetoxymethyl, carbamoyloxymethyl, or thiadiazolylthiomethyl as R^5 and salts of these. It is to be noted that compounds (I) having a single bond, dimethylene, or trimethylene as R^2 or that having no carboxylic 7-beta-side chain are practically unabsorbed enterally. A compound having amino in R can form a salt by mixing with an acid, e.g., mineral acid (e.g. HCl), carboxylic acid (TFA).

EXAMPLES

Following examples illustrate the embodiments of this invention.

In the Examples, "part" shows part by weight and "equivalent" shows molar equivalent of the beta-lactam

starting material. Symbols "cis" and "trans" show relative position of amido and carboxylic substituents attaching to the side chain double bond. Physicochemical constants of the products are summarized in Tables in which IR shows cm^{-1} value, NMR shows δ -value, and J value shows coupling constants in Hz scale. In NMR of a geometric isomer mixture, signals splitting into two or more are shown by chemical shifts separating with comma and splitting number and "X" before multiplicity mark.

Usually the reaction mixture is, if required after adding a solvent (e.g., water, acid, dichloromethane), washed, dried, and concentrated, and the product is separated. All concentrations are done in reduced pressure. (Abbreviations) AOM=acetoxymethyl; BH=diphenylmethyl; Bu=butyl; BOC=t-butoxycarbonyl; Bzl=benzyl; Cbz=benzyloxycarbonyl; circle in a hetero ring of the structural formula=the ring is aromatic; exo=3,4-double bond position isomer in the 7-side chain acyl; Me=methyl; MEM=methoxyethoxymethyl; Ph=phenyl; PMB=p-methoxybenzyl; PNB=p-nitrobenzyl; and POM=pivaloyloxymethyl.

EXAMPLE 1 (Sodium salt)

(1) A solution of carboxylic acid (1) in Table 2 (1 g) in aqueous 0.5% sodium hydrogen carbonate (6 ml) adjusted to pH 7 with hydrochloric acid is washed with ethyl acetate, desalted, and poured into a 10 ml vial. This is lyophilized conventionally to give the corresponding sodium salt (2) as powder.

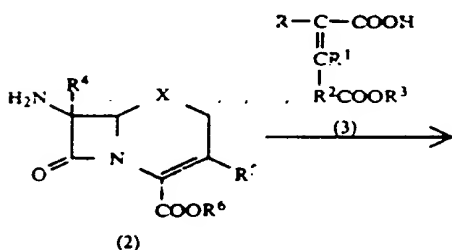
(2) Similarly, to a suspension of carboxylic acid (1) (1 g) of Table 2 in water is added aqueous sodium carbonate to make a solution of pH 6.5. The solution is desalted and poured into 10 ml vials, and lyophilized to give a sodium salt preparation same to above.

(3) The sodium salt (1 g) produced under sterile condition is dissolved in sterile water (4 g) and is given twice a day orally or intravenously to a patient suffering from *Staphylococcus aureus* infection for treating said disease.

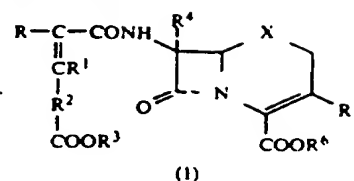
(4) Each one of the carboxylic acids on Table 2 are dissolved in aqueous sodium hydrogen carbonate and assayed as the sodium salts for MIC by the standard method of Japan Society of Chemotherapy to give values of 3.1 to 0.2 microgram/ml against *Streptococcus pyogenes* C-203 and 0.8 to 0.025 microgram/ml against *Escherichia coli* H.

EXAMPLE 2 (Amidation)

A 7-beta-amino compound (2) (1 equivalent) is treated with carboxylic acid corresponding to the 7-beta-side chain (3) or its reactive derivative to give a side (1), for a method as exemplified below:



-continued



(1) In a mixture of dichloromethane (10 volumes), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.1 equivalents) N,N'-dicyclohexylcarbodiimide (1.1 equivalents), pyridine (1.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 6 hours at 0° C. to room temperature.

(2) In a mixture of ethyl acetate (10 volumes), di-2-pyridyl disulfide (1.1 equivalents), triphenylphosphine (1.1 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 2 to 6 hours at 10° to 50° C.

(3) In a mixture of dichloromethane (3 volumes), 1,3,5-tripyrindiniumtriazine trichloride (4 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at -10° to 10° C.

(4) In a mixture of carbon tetrachloride (30 volumes), 4-methylmorpholine (1.5 equivalents), trisdiethylaminophosphine (1.1 equivalents) and carboxylic acid (3) (1.1 equivalents), kept at -20° to 10° C. for 1 to 5 hours.

(5) In a mixture of chloroform (10 volumes) and dimethoxyethane (10 volumes), triethylamine (1.5 moles), and a mixed anhydride of carboxylic acid (3) and isobutoxyformic acid, stirred at a temperature between -5° to 10° C. over a 30 minutes and 6 hours time.

(6) In a mixture of ethyl acetate (10 volumes), 1,2-dichloroethane (10 volumes), 4-methylmorpholine (1.5 equivalents), and the symmetric anhydride of carboxylic acid (3) (1.1 equivalents), refluxed for 10 minutes to 2 hours.

(7) In a mixture of dichloromethane (10 volumes), pyridine (1.5 equivalents), and mixed anhydride of carboxylic acid (3) and methanesulfonic acid (1.1 equivalents), stirred for 1 to 3 hours at between -70° C. and room temperature.

(8) In a mixture of ethyl acetate (10 volumes), pyridine (1.5 equivalents) and a mixed anhydride of diethyl hydrogen phosphate and carboxylic acid (3) (1.5 equivalents), stirred at 0° C. to 10° C. for 1 to 5 hours.

(9) In a mixture of ethyl acetate (10 volumes), dichloromethane (10 volumes), N-methylmorpholine (1 equivalent), and mixed anhydride of carboxylic acid (3) and dichlorophosphoric acid (1.1 equivalents), stirred for 1 to 3 hours at 0° C. to room temperature.

(10) In a mixture of lutidine (1.5 equivalents), dichloromethane (10 volumes), and the mixed anhydride (1.1 to 2 equivalents) of carboxylic acid (3) and monochlorophosphoric acid dimethylamide, stirred for 1 to 4 hours at 0° to 30° C.

(11) In a mixture of dichloromethane (5 volumes), trifluoroacetic anhydride (1.5 equivalents), pyridine (3 equivalents), and carboxylic acid (3) (1.5 equivalents), stirred for 1 to 5 hours at 0° to room temperature.

(12) In a mixture of dichloromethane (10 volumes), bromide of diethyl hydrogen phosphate (1.2 equivalents), 4-methylmorpholine (2.5 equivalents), and carboxylic acid (3) (1.2 equivalents), stirred for 1 to 3 hours at 0° C. to room temperature.

(13) Amine (2) having carboxy at position 4 of the cephem ring is dissolved in aqueous (10 volumes) so-

dium hydrogen carbonate (2.5 equivalents). Carboxylic acid (3) chloride (1.1 equivalents) is dropwise added thereto. The mixture is kept at -5°C . to room temperature for 30 minutes to 2 hours.

(14) Amine (2) having carboxy at position 4 of the cephem ring is treated with trimethylsilyl chloride and triethylamine (1.2 equivalents each), and then treated with pyridine (4 equivalents) and carboxylic acid (3) chloride (1.1 equivalents) at -30°C . for between 30 minutes and 2 hours, and then the resulting silyl ester is hydrolyzed with acid.

(15) In a solution of picoline (4 equivalents) and carboxylic acid (3) chloride (1.2 equivalents) in dichloromethane (20 volumes) stirred at 0°C . to -30°C . over 30 minutes and 2 hours.

(16) In a mixture of dimethylformamide (2 volumes) and ethyl acetate (10 volumes), stirred with triethylamine (1.1 equivalents) and carboxylic acid (3) chloride (1.1 equivalents) at 0°C . to 20°C . for between 30 minutes and 3 hours.

(17) In a mixture of dichloromethane (30 volumes), cyanuric chloride (1.1 equivalents), pyridine (4 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 5 minutes to 2 hours at -30°C . to 10°C .

(18) In a mixture of dichloromethane (3 volumes), phosphorus oxychloride (1.1 equivalents), triethylamine (1.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 20 minutes to 2 hours at -10°C . to 10°C .

(19) Amine (2) is treated with trimethylsilyl chloride and an acid scavenger to obtain the corresponding N-trimethylsilyl compound, and this is treated with phosphorus oxychloride (1.5 equivalents), carboxylic acid (3) (1.2 equivalents), and dimethylaniline (4 equivalents) in dichloromethane (5 parts) for 30 minutes to 2 hours at 0°C . to room temperature.

(20) In a mixture of dichloromethane (8 volumes), thionylchloride (1.5 equivalents), pyridine (2.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at -30° to 0°C .

(21) In a mixture of chloroform (3 volumes), toluene (1 volume), picoline (2 equivalents), oxalyl chloride (1 equivalent), and carboxylic acid (3) (1.1 equivalents), stirred for 10 minutes to 2 hours at -50°C . to 10°C .

(22) In a mixture of dichloromethane (20 volumes), pyridine (3 equivalents), and benzotriazolyl ester of carboxylic acid (3) (3 equivalents), stirred for 5 to 30 hours at 10° to 50°C .

(23) In a mixture of dichloromethane (20 volumes), 2-ethoxy-1-methoxycarbonyl-1,2-dihydroquinoline (2.5 equivalents) and carboxylic acid (3) (2 equivalents), stirred at room temperature for 1 to 15 hours.

(24) In a mixture of dioxane (10 volumes) and phthalimido ester of carboxylic acid (3) (2 equivalents), stirred for 2 to 8 hours at 10° to 50°C .

(25) In a mixture of methyl isobutyl ketone (10 volumes) and succinimido ester of carboxylic acid (3) (1.5 equivalents), stirred for 2 to 9 hours at 0° to 40°C .

(26) In a mixture of carbonyldiimidazole (1.1 equivalents), tetrahydrofuran (19 volumes), dimethylacetamide (5 volumes), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at 0°C . to room temperature.

(27) In a mixture of dimethylformamide (5 volumes), dimethylaniline (1.3 equivalents), carboxylic acid (3), and the Vilsmeier reagent made from dimethylformamide (1.1 equivalents), stirred at room temperature for 1 to 5 hours.

(28) In a mixture of dichloromethane (10 volumes), dimethylformamide (5 volumes), N,N'-dicyclohexylcarbodiimide (1.1 equivalents), picoline (1.2 equivalents), and carboxylic acid (3) (1.1 equivalents), reacted for 2 hours to 24 hours.

(29) To a solution of 7-amino-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester in dichloromethane (50 parts) containing 2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenic acid (1 equivalent) is added N,N'-dicyclohexylcarbodiimide (1 equivalent). After stirring for 2 hours at room temperature, the mixture is concentrated. The residue is triturated in ethyl acetate, filtered to remove solid, and purified by column chromatography to give 7-[2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenylamino]-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester. Yield, 90%.

(30) To a solution of 7-amino-3-pyridiniummethyl-3-cephem-4-carboxylic acid chloride hydrochloride in a mixture of water (10 parts) and dioxane (15 parts) are added at 0°C . sodium hydrogen carbonate (2 equivalents), 2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenic acid (1.2 equivalents), 1-hydroxybenzotriazole (1.2 equivalents), N,N'-dicyclohexylcarbodiimide (1.2 equivalents), and dioxane (5 parts) at 0°C . After stirring at 0°C . for 3.5 hours, the mixture is acidified with 1N-hydrochloric acid (5 parts) and filtered. The filtrate and acetone (50 parts) washing of the solid are combined, purified by silica gel chromatography, and lyophilized to give 7-[2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenylamino]-3-pyridiniummethyl-3-cephem-4-carboxylate. Yield: 50.8%.

EXAMPLE 3 (Carboxy-Deprotection)

(1) A solution of a t-butyl, p-methoxybenzyl, or diphenylmethyl ester of Table 1 in a mixture of dichloromethane (0.3 to 3 parts), trifluoroacetic acid (0.3 to 3 parts), and anisole (0.5 to 5 parts) is stirred for 10 minutes to 3 hours at between -10° and 40°C . The solution is concentrated to remove the solvent and reagent. The residue is washed with benzene or ether to give the corresponding acid in 70 to 90% yield.

(2) To a solution of a t-butyl, benzyl, p-methylbenzyl, p-methoxybenzyl, or diphenylmethyl ester listed in Table 1 in a mixture of dichloromethane (5 to 9 parts) and anisole (2 to 8 parts) is added aluminum chloride, tin tetrachloride, or titanium tetrachloride (3 to 12 equivalents) at between -10° and 10°C ., and the mixture is stirred for 1 to 24 hours. The mixture is washed with diluted hydrochloric acid and water, dried and concentrated to give the corresponding free acid in 80 to 95% yield. t-Butoxycarbonylamino, N-t-butoxycarbonyl-N-methoxyethoxymethylamino, or benzoyloxycarbonylamino group when present, is deprotected to give amino group.

(3) To a solution of a t-butyl, benzyl, p-methylbenzyl, p-methoxybenzyl, or diphenylmethyl ester listed on Table 1 are added 90% formic acid (5 to 6 parts) and anisole (2 to 3 parts). The mixture is stirred at 50° to 60°C . for 1 to 4 hours to give the corresponding carboxylic acid in 40 to 50% yield.

(4) To a solution of a p-nitrobenzyl ester of Table 1 in dichloromethane (60 parts) are added acetic acid (10 parts) and zinc powder (2 parts). After stirring for 2 hours at 0°C ., the mixture is filtered to remove solid, diluted with water, and extracted with dichloromethane.

ane. The extract solution is washed with water and extracted with aqueous sodium hydrogen carbonate. The aqueous layer is washed with hydrochloric acid to pH 2, and extracted with dichloromethane. This organic layer is washed with water, dried, and vacuum concentrated to give the corresponding free acid in 60 to 80% yield.

(5) The same ester can be deesterified by shaking with hydrogen in the presence of the same amount of 5% palladium charcoal in dioxane at room temperature for 2 hours.

(6) To a solution of 7-[2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenoylamino]-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester in anisole (12 parts) is added aluminum chloride (9 equivalents). After stirring for 4 hours at 0° C., the mixture is neutralized with aqueous 5% sodium hydrogen carbonate, filtered to remove solid, and washed with ethyl acetate. Aqueous layer is acidified with hydrochloric acid, washed with ethyl acetate, and passed through a column of HP 20 or SP 207 (synthetic adsorbent produced by Mitsubishi Chemical K.K.). Adsorbed material is eluted with 80% methanol to afford 7-[2-(2-amino-4-thiazolyl)-4-carboxy-2-butenoylamino]-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid. Yield: 65%.

(7) To a suspension of 7-[2-(2-benzoyloxycarbonylamino-4-thiazolyl)-4-benzoyloxycarbonyl-2-butenoylamino]-3-pyridiniummethyl-3-cephem-4-carboxylic acid in anisole (2 parts) is added a solution of aluminum chloride (9 equivalents) in anisole (2 parts) at 0° C. After stirring for 3.5 hours, the mixture is acidified with 10% hydrochloric acid and washed with ethyl acetate. Aqueous layer is passed through a column of Diaion HP-20. Adsorbed material is eluted with aqueous 5% acetone and the eluate lyophilized to give 7-[2-(2-amino-4-thiazolyl)-3-carboxymethylacrylamido]-3-pyridiniummethyl-3-cephem-4-carboxylic acid. Yield: 55%.

(8) In a manner similar to that of above (1) to (7), a free carboxy compound of Table 2 are prepared from the corresponding carboxy-protected compound of Table 1.

(9) To a solution of diphenylmethyl 7beta-[2-(2-carbobenzoxaminothiazol-4-yl)-4-allyloxycarbonyl-2-butenoylamino]-3-cephem-4-carboxylate (3.75 g) (5 mM) in dichloromethane (30 ml) are added 2-ethylhexanoate (1.5 molar equivalents), triphenylphosphine (0.5 equivalents), and tetrakis(triphenylphosphine)-palladium complex (125 mg). After stirring for 1 hour at 2° C, the mixture is diluted with ether to separate diphenylmethyl 7beta-[2-(2-carbobenzoxaminothiazol-4-yl)-4-sodiooxycarbonyl-2-butenoylamino]-3-cephem-4-carboxylate in 94% yield. This is suspended in water (10 parts) and acidified with aqueous 4% phosphoric acid to separate diphenylmethyl 7beta-[2-(2-carbobenzoxaminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylate.

EXAMPLE 4 (Amino deprotection)

(1) A solution of a t-butoxycarbonylamino compound listed on Table 1 in a mixture of dichloromethane (0.3 to 3 parts), trifluoroacetic acid (0.3 to 3 parts), and anisole (0.5 to 5 parts) is stirred for 10 minutes to 3 hours at between -10° and 40° C. The solution is concentrated to remove the solvent and reagent. The residue is washed with benzene to give the corresponding amino compound listed on Table 1 or 2 in 70 to 80% yield.

(2) To a solution of a t-butoxycarbonylamino, benzoyloxycarbonylamino, methylbenzyloxycarbonylamino, methoxyethoxymethylamino, or tritylamino compound listed in Table 1 (1 part) in a mixture of dichloromethane (5 to 9 parts) and anisole (2 to 8 parts) is added aluminum chloride, tin tetrachloride, or titanium tetrachloride (3 to 12 equivalents) at between -10° and 10° C., and the mixture is stirred for 1 to 24 hours. The mixture is extracted with diluted hydrochloric acid and water, the aqueous layer is passed through a column of HP-20 absorbent to give the corresponding free amino compound listed on Table 1 or 2 in 60 to 80% yield. A t-butyl, benzyl, p-methylbenzyl, p-methoxybenzyl, or diphenylmethyl ester group when present, is deprotected to give free carboxy.

(3) To a solution of a chloroacetamido compound of Table 1 in a mixture of tetrahydrofuran (15 parts) and methanol (15 parts) are added thiourea or N-methyldithiocarbamate (4 equivalents) and sodium acetate (2 equivalents). After one night at room temperature, the mixture is concentrated, diluted with ethyl acetate, washed with saline, dried, and concentrated. The residue is chromatographed to give the corresponding amino compound.

(4) To a solution of a formamide, Schiff base, silylamino, or tritylamino compound listed on Table 1 in formic acid, acetic acid, or ethanol (10 parts) is added 1 to 3N-hydrochloric acid (0.1 to 3 parts), and the mixture is stirred for 1 to 3 hours at room temperature. The reaction mixture is concentrated, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate and water, dried and concentrated. The residue is purified in a conventional manner to give the corresponding free amino compound listed on Table 1 or 2.

(5) To a solution of a benzoyloxycarbonylamino compound listed on Table 1 in a mixture of ethanol and ethyl acetate (30 parts: 1:1) is added 5% palladium charcoal (0.5 parts), and the mixture is shaken under hydrogen until the starting material is consumed. The reaction mixture is filtered to remove solid and concentrated to give the corresponding amino compound listed on Table 1 or 2.

EXAMPLE 5 (Esterification)

(R³ and/or R⁶=diphenylmethyl)

(1) To a solution of compound (I) in which R³ and/or R⁶ is hydrogen in a mixture of dichloromethane and methanol (10 weights each) is added diphenyldiazomethane (2 equivalents). After stirring for 1 hour, the mixture is washed with hydrochloric acid and water, dried, and concentrated. The residue is crystallized from ethyl acetate to give the corresponding diphenylmethyl ester.

(R³ and/or R⁶=POM)

(2) To a solution of compound (I) wherein R³ and/or R⁶ is potassium in N,N-dimethylformamide (2 to 5 parts) is added iodomethyl pivalate (1 to 2 equivalents) under ice-salt cooling. After 15 minutes to 2 hours stirring, the mixture is diluted with ethyl acetate, washed with ice water and aqueous sodium hydrogen carbonate, dried, and concentrated in vacuum. The residue is recrystallized from ethyl acetate to give the pivaloyloxymethyl ester of the carboxylic acid of Table 1.

(3) The potassium salt of above section (2) is replaced by sodium salt to give the same products under the same condition.

(4) The pivaloyloxymethyl ester of above section (2) (250 mg), corn starch (150 mg), and magnesium stearate (5 mg) are mixed, granulated, and encapsulated in a conventional manner. This capsule (b 2 to 3 capsules) are given orally to treat a patient suffering from infection caused by sensitive *E. coli*.

(R³ and/or R⁶=AOM)

(5) In place of iodomethyl pivalate of above (2), iodomethyl acetate is used under the same reaction condition to give the corresponding acetoxyethyl ester of Table 3.

EXAMPLE 6 (Introduction of 3-substituents)

(R⁵=H)

(1) To a solution of a compound listed on Table 1 and having methanesulfonyloxy or chlorine as R⁵ in dichloromethane (13 parts) are added acetic acid (10 part) and zinc powder (2.5 parts) and the mixture is heated at 50° C. for 5 hours. The reaction mixture is filtered to remove solid, diluted with ethyl acetate, washed with diluted hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residue is purified by silica gel chromatography eluting with a mixture of benzene and ethyl acetate to give the corresponding compound listed on Table 1 or 2 having hydrogen as R⁵ in 50 to 80% yield.

(2) Above reaction (1) is carried out at room temperature for 5 to 10 hours in the presence of a diluent isopropanol (4 parts) to give the same product in 40 to 60% yield.

(3) To a solution of 7beta-[2-(2-benzoyloxycarbonylaminothiazol-4-yl)-4-benzoyloxycarbonylbut-2-enoylamino]-3-hydroxycephem-4-carboxylic acid diphenylmethyl ester sulfoxide in dichloromethane (13 parts) are added pyridine (6 equivalents) and acetic anhydride (6 equivalents). After 13 hours' stirring at 0° C., the mixture is mixed with triethylamine (3 equivalents) and stirred for 24 hours. The reaction mixture is washed with water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated to give 7beta-[2-(2-benzoyloxycarbonylaminothiazol-4-yl)-4-benzoyloxycarbonyl-2-butenoylamino]-3-cephem-4-carboxylic acid diphenylmethyl ester sulfoxide in 40 to 60% yield.

(R⁵=cyanomethylthiomethyl)

(4) In the manner as given in Preparation B-4 a compound having bromomethyl as R⁵ is treated with sodium cyanomethyl mercaptide at -65° C. to 70° C. for 2 hours to give the corresponding compound listed on Table 1 having cyanomethylthiomethyl as R⁵ in 50 to 60% yield.

EXAMPLE 7 (Sulfoxide reduction)

In a manner similar to that of Preparation B-4(2) using the same ratio of the reagents and solvents, the corresponding sulfoxide is reduced to give the cephem (sulfide) compounds of Table 1.

EXAMPLE 8 (Double bond migration)

A solution of 7beta-[2-(2-*t*-butoxycarbonylaminothiazol-4-yl)-4-benzoyloxycarbonyl-2-butenoylamino]-3-chloro-2-cephem-4-carboxylic acid diphenylmethyl ester is reduced according to the method of Example (1) to induce concomitant double bond migration affording 7beta-[2-(2-aminothiazolyl-4-yl)-4-carboxy-2-

butenoylamino]-3-cephem-4-carboxylic acid diphenylmethyl ester in 53% yield.

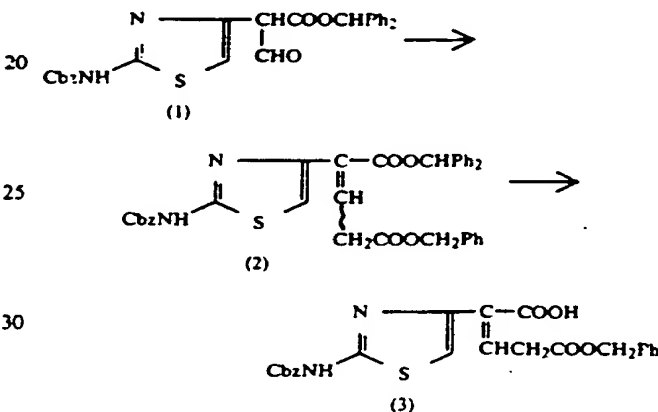
EXAMPLE 9 (Amine salt)

To a solution of an amino compound listed on Table 2 in diluted hydrochloric acid is added acetonitrile. The precipitated material is collected by filtration to give the corresponding hydrochloric acid addition salt in good yield.

PREPARATIONS A PREPARATION OF CARBOXYLIC ACIDS

Preparation A-1

15 2-(2-Benzoyloxycarbonylaminothiazol-4-yl)-4-benzoyloxycarbonyl-2-butenic acid (3)



(1) A solution of formylacetate (1) and benzoyloxycarbonylmethylidenetriphenylphosphorane (1.3 equivalents) in dioxane or toluene (8 parts) is stirred for 1 to 6 hours at 80° to 120° C. After cooling, the mixture is concentrated, and the residue is purified by silica gel chromatography to give propendicarboxylate (2). Yield: 87%. This is a mixture of 34% cis and 53% trans geometric isomers which can be separated after repeated chromatography.

IR (CHCl₃) ν : 3410, 1730 cm⁻¹ (trans).

IR (CHCl₃) ν : 3400, 1730 cm⁻¹ (cis).

(2) To a solution of this product (2) in dichloromethane (10 parts) are added anisole (2 parts) and trifluoroacetic acid (2 parts). After stirring for 2 hours, the reaction mixture is concentrated, and the residue washed with a mixture of ether and hexane to give monobenzyl ester of the dicarboxylic acid (3). Yield: 89%. These geometric isomers can be separated by chromatography.

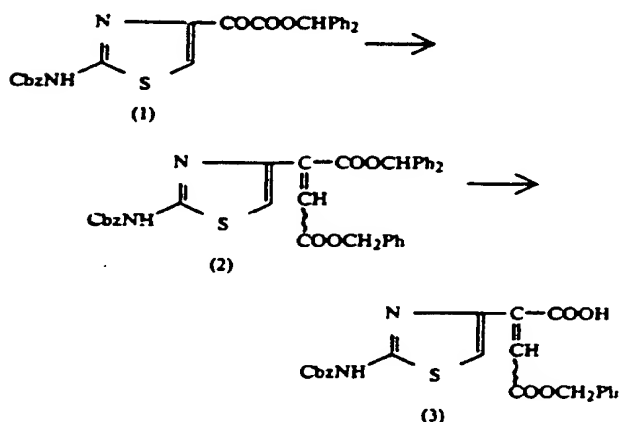
NMR (CDCl₃-CD₃OD) δ : 3.51 (d, J=7 Hz, 2H), 5.13 (s, 2H), 5.26 (s, 2H), 7.06 (s, 1H), 7.0-7.5 (m, 11H) (trans).

NMR (CDCl₃-CD₃OD) δ : 3.73 (d, J=7 Hz, 2H), 5.13 (s, 2H), 7.10 (s, 1H), 7.0-7.5 (m, 11H) (cis).

In a manner similar to that of Preparation A-1, a butenoic acid diester listed on Table 4 is prepared from the corresponding formylacetate using the same ratios of reactants and solvents at the same temperature for the same reaction time. The obtained ester is, if required, totally or partially deesterified using a conventional reagent, e.g., sodium hydroxide for alkyl esters and a Lewis acid (e.g., aluminum, titanium, or tin halide) for *t*-alkyl or aralkyl esters, to give free acids.

Preparation A-2

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-3-benzyloxycarbonyl-2-propenoic acid (3)



(1) A solution of 2-oxoacetate (1) and benzyloxycarbonylmethylidencitriphenylphosphorane (1.25 equivalents) in toluene or dioxane (10 parts) is refluxed for 1 to 3 hours. The mixture is concentrated and the residue purified by silica gel chromatography to give diester (2). Yield: 95%.

NMR (CDCl_3) δ : 5.12 (s, 4H), 7.00 (s, 1H), 7.07 (s, 1H), 7.1-7.5 (m, 21H).

This product is a mixture of cis-trans isomers at the double bond.

(2) The product (2) is dissolved in dichloromethane (7 parts) and mixed with trifluoroacetic acid (1 part) and anisole (1 part). After stirring for 7 hours at 0° C., the mixture is concentrated and triturated in a mixture of ether and hexane and then in a mixture of ether and methanol to give monoester (3), trans isomer. Yield: 83%.

IR (Nujol) ν : 1730, 1710, 1695 cm^{-1} .

NMR ($\text{CDCl}_2 + \text{CD}_3\text{OD}$) δ : 5.17 (s, 2H), 5.21 (s, 2H), 7.07 (s, 1H), 7.2-7.5 (m, 11H) ppm.

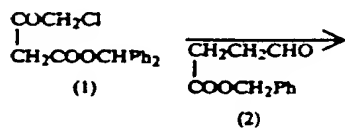
(3) This trans isomer (3) is dissolved in tetrahydrofuran (10 parts) and mixed with phosphorus pentachloride (1.12 equivalents). After stirring for 2 hours at 0° C., the mixture is neutralized with aqueous 5% sodium hydrogen carbonate (80 ml) and stirred at room temperature. Separated crystals are collected by filtration, washed with ethyl acetate and water, suspended in water, acidified with hydrochloric acid, and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated. The residue is crystallized from a mixture of ether and hexane to give monoester (3), cis isomer. Yield: 47%. mp. 144°-146° C.

IR (CHCl_3) ν : 3410, 1720 cm^{-1} .

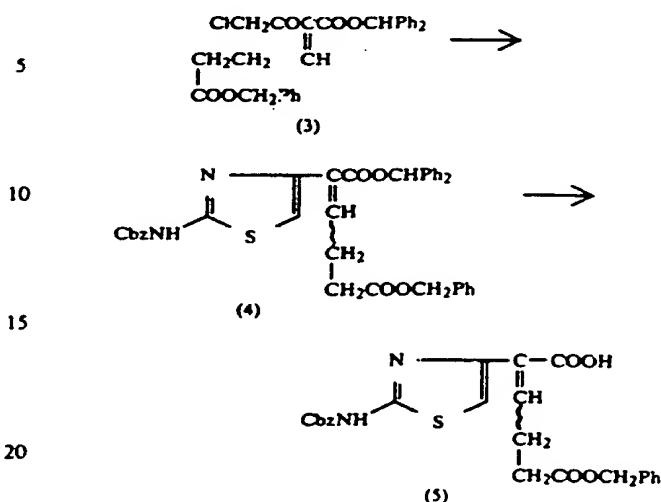
NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ : 5.18 (s, 2H), 5.21 (s, 2H), 6.62 (s, 1H), 7.15 (s, 1H), 7.32 (s, 5H), 7.35 (s, 5H) ppm.

Preparation A-3

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-5-benzyloxycarbonyl-2-pentenoic acid (5)



-continued



(1) A mixture of 4-chloroacetoacetic acid benzhydryl ester (1) (6.95 g), aldehyde (2) (3.9 g), benzene (35 ml), piperidine (0.79 ml), and acetic acid (0.24 mg) is heated at 50° C. for 3 hours. The mixture is washed with water, aqueous saturated sodium hydrogen carbonate, water, 0.5N-hydrochloric acid, and water, dried over magnesium sulfate, and concentrated. The residue is subjected to silica gel chromatography (eluting with benzene) to give a mixture of cis and trans (1:1) isomers of the product (3) (5.7 g).

(2) To a solution of this product (3) in ethanol (30 ml) is added thiourea (1.1 g). After heating at 50° C. for 2 hours, the mixture is washed with aqueous saturated sodium hydrogen carbonate and concentrated. The residue is dissolved in dichloromethane (20 ml) and mixed with pyridine (0.536 ml) and benzyl chloroformate (0.757 ml) at 0° C. After 1.5 hours' stirring at 0° C., the mixture is washed with water, dried over magnesium sulfate, and concentrated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (20:1) mixture) to give aminothiazole ester (4), cis isomer (467 mg) and trans isomer (600 mg).

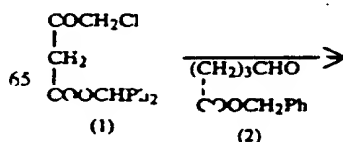
(cis isomer)=IR (CHCl_3) ν : 3400, 1720, 1540, 1440, 1385, 1280, 1160 cm^{-1} .

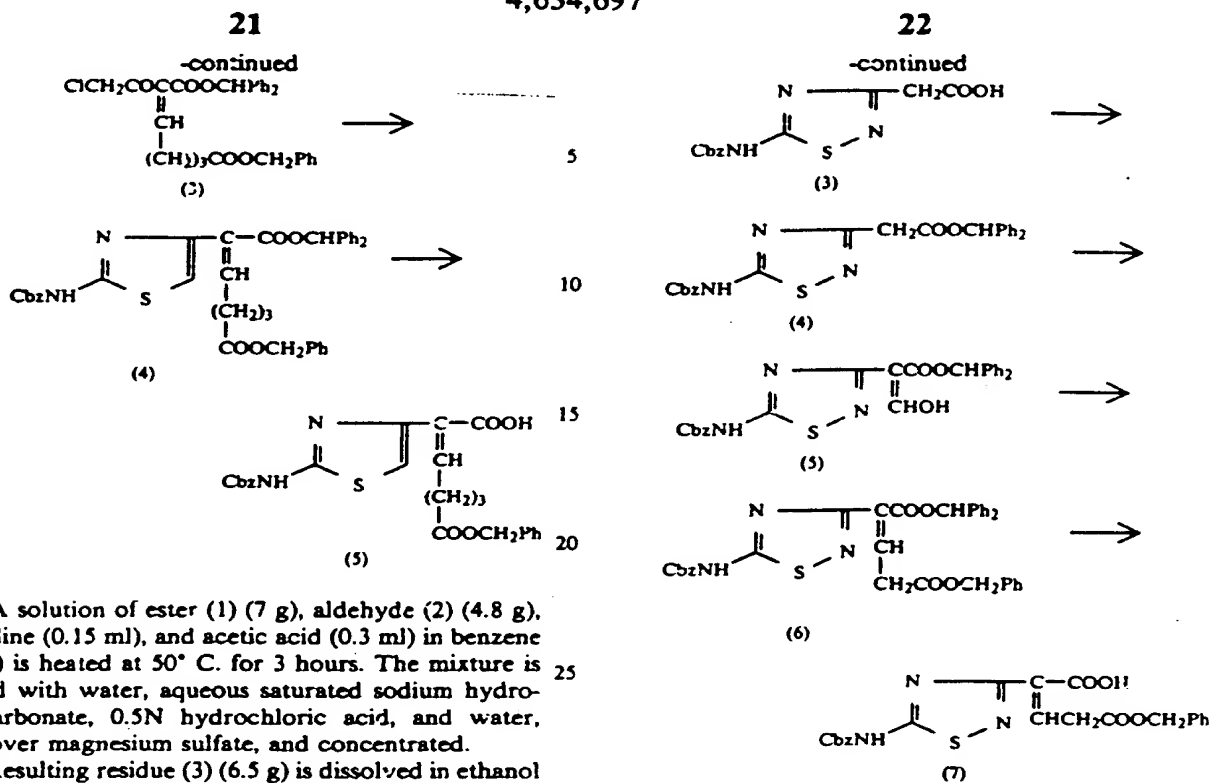
(trans isomer)=IR (CHCl_3) ν : 3400, 1720, 1540, 1440, 1385, 1280, 1160 cm^{-1} .

(3) To the isomers of aminothiazole ester (4) respectively are added dichloromethane, anisole (1 part), and trifluoroacetic acid (2 parts). After 2 hours stirring at 0° C., the mixture gives each isomer of the corresponding dicarboxylic acid monobenzyloxy ester (5).

Preparation A-4

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-6-benzyloxycarbonyl-2-hexenoic acid (5)





(1) A solution of ester (1) (7 g), aldehyde (2) (4.8 g), piperidine (0.15 ml), and acetic acid (0.3 ml) in benzene (40 ml) is heated at 50° C. for 3 hours. The mixture is washed with water, aqueous saturated sodium hydrogen carbonate, 0.5N hydrochloric acid, and water, dried over magnesium sulfate, and concentrated.

(2) Resulting residue (3) (6.5 g) is dissolved in ethanol (35 ml), mixed with thiourea, and heated at 50° C. for 2 hours. The mixture is washed with aqueous saturated sodium hydrogen carbonate and concentrated. The residue is dissolved in dichloromethane (20 ml), mixed with pyridine (0.754 ml) and benzyl chloroformate (1 ml), and stirred at 0° C. for 1.5 hours. The reaction mixture is washed with water, dried, and concentrated. The residue is separated by silica gel chromatography (eluting with benzene-ethyl acetate (20:1) mixture) to give thiazole ester (4) [trans isomer (470 mg) and trans-

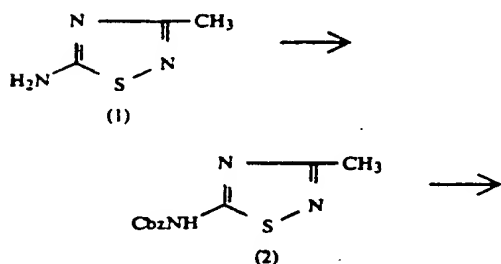
(trans-Thiazole ester (4)): IR (CHCl₃) ν : 3400, 3000, 1720, 1540, 1440, 1370, 1280, 1150 cm⁻¹.

(cis-Thiazole ester (4)): IR (CHCl₃) ν : 3400, 3000, 1720, 1540, 1440, 1370, 1280, 1150 cm⁻¹.

(3) Thiazole ester (4) (470 mg) as produced above (1) is dissolved in dichloromethane (15 ml), mixed with anisole (0.611 ml) and trifluoroacetic acid (1.22 ml), and stirred at 0° C. for 2 hours. After concentrating to dryness, the mixture is triturated in a mixture of ether and hexane (1:1) to give thiazolecarboxylic acid (5) (336 mg).

Preparation A-5

2-(5-Benzyloxycarbonylamino-1,2,4-thiadiazol-3-yl)-4-benzyloxycarbonyl-2-butenic acid (7)



(1) Amine (1) (6 g) is amidated with benzyl chloroformate (1.2 equivalents) in dichloromethane (120 ml) containing pyridine (2.5 equivalents) at 0° C. for 2 hours to give carbamate (2) (11.2 g). mp. 157°-158° C. Yield: 94.6%.

(2) To a solution of diisobutylamine (25.2 ml) in tetrahydrofuran (125 ml) cooled at -30° C. to -5° C. is added 1.6 N n-butyllithium hexane solution (112.3 ml) over 21 minutes period. After 1 hour 20 minutes' stirring at 0° C., the mixture is mixed with a solution of carbamate (2) (11.2 g) in tetrahydrofuran (150 ml) at -68° C. to -64° C. over 1 hour 20 minutes, and stirred at the same temperature for 3 hours. This is quenched with dry ice (200 g) and warmed gradually up to -5° C. The reaction mixture is diluted with water (150 ml), washed with ethyl acetate, acidified with 2N-hydrochloric acid to pH 2, and extracted with dichloromethane. The extract solution is washed with water, dried, concentrated, and diluted with ether to afford acetic acid (3) (6.33 g). mp. 172°-173° C.

(3) To a solution of acetic acid (3) (7 g) in methanol (200 ml) is added diphenyldiazomethane until none of the acetic acid (3) is detectable. The mixture is concentrated to give Ester (4). mp. 144°-146° C.

(4) To a solution of ester (4) (4.1 g) and diphenylmethyl formate (3.03 g) in tetrahydrofuran (41 ml) cooled at 0° C. is added 60% sodium hydride (1.1 g). After 2 hours 20 minutes' stirring at 60° C., the mixture is diluted with water, acidified with 2N-hydrochloric acid, and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated to give aldehyde (5) (2.75 g). Yield: 63.5%.

IR (CHCl₃) ν : 3140, 1720, 1610, 1540, 1280, 1080 cm⁻¹.

(5) A solution of aldehyde (5) (781 mg) and benzyloxycarbonylmethylidenephosphorane (985 mg) in dioxane (17 ml) is refluxed for 3 hours. The mixture is concen-

trated to give acrylate (6) (631 mg). Yield: 63.5%. A cis/trans (4:6) mixture.

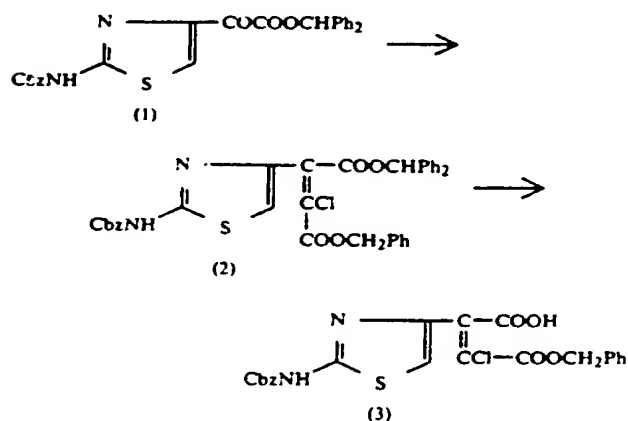
IR (CHCl₃): ν : 3150, 1730, 1545, 1280 cm⁻¹.

(6) To a solution of acrylate (6) (309 mg) in dichloromethane (4.5 ml) are added anisole (0.3 ml) and trifluoroacetic acid (0.6 ml). After 1 hour's stirring at room temperature, the mixture is diluted with hexane to give half ester (7) (171 mg). Yield: 75.7%. This is a cis/trans (1:6.45) mixture.

IR (CHCl₃) ν : 1730, 1621, 1540, 1230 cm⁻¹.

Preparation A-6

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-3-chloro-3-benzyloxycarbonyl-2-propenoic acid (3)

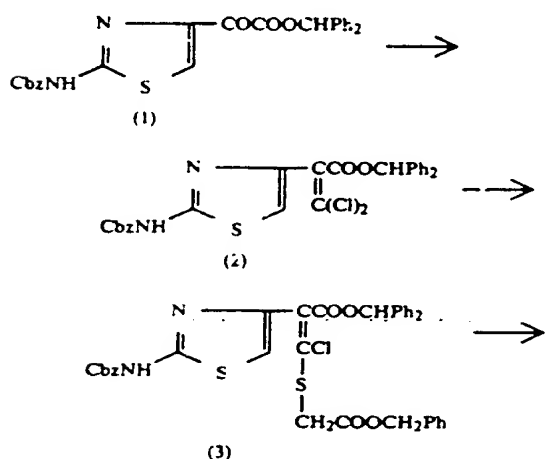


(1) A solution of ketone (1) (472 mg) and benzyloxycarbonylchloromethylenetriphenylphosphorane (467 mg) in benzene (5 ml) is heated at 60° C. for 30 minutes and concentrated. The residue is crystallized from a mixture of ether and pentane to give chloroethylene (2) (393 mg). Yield: 61%.

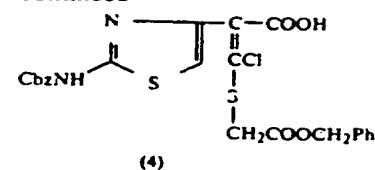
(2) A solution of chloroethylene (2) (270 mg) in a mixture of anisole (2 parts) and trifluoroacetic acid (1 part) is let stand for 15 minutes and concentrated to give half ester (3) (190 mg). Yield: 95%.

Preparation A-7

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-3-benzyloxycarbonylmethylthio-3-chloro-2-propenoic acid (4)



-continued



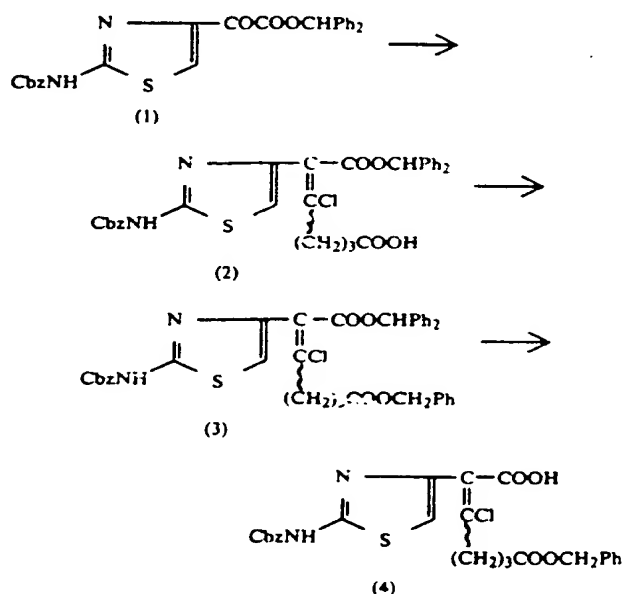
(1) Ketone (1) and dichloromethylidenetriphenylphosphorane are reacted in a manner as described in Japanese Patent Application Kokai No. 57-67581 to give dichloroethylene (2).

(2) To an ice cold solution of dichloroethylene (2) (395 mg) in N,N-dimethylformamide (3 ml) are added benzyl thioglycolate (200 mg) and triethylamine (153 mg) under nitrogen. After stirring for 45 minutes, the mixture is diluted in ethyl acetate, washed with water, dried, and concentrated. The residue is purified by chromatography to give thioether (3) (326 mg). Yield: 64%.

(3) A solution of thioether (3) in a mixture of trifluoroacetic acid (2 parts) and anisole (2 parts) is let stand for 20 minutes and concentrated to give half ester (4). Yield: 88%.

Preparation A-8

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-3-chloro-6-benzyloxycarbonyl-2-hexenoic acid (4)



(1) To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (887 mg) in tetrahydrofuran (3.5 ml) is added 1M-lithium bistrimethylsilylamide (4.2 ml). After 15 minutes' stirring at room temperature, this solution is dropwise added to a suspension of iodobenzene-dichloride (605 mg) in tetrahydrofuran at -78° C. After 10 minutes at -78° C., lithium bistrimethylsilylamide (2.2 ml) is added to the mixture. To this solution is added a solution of ketoester (1) (378 mg) in tetrahydrofuran (2 ml). The mixture is stirred at -78° C. for 10 minutes and at room temperature for 1 hour, diluted with diluted hydrochloric acid, and extracted with ethyl acetate. The extract solution is dried and concentrated. The residue is purified by silica gel chromatography.

phy (eluting with dichloromethane and ethyl acetate (1:1) mixture) to give vinylcarboxylic acid (2) (250 mg).

IR (CHCl₃) ν : 1715, 1540 cm⁻¹.

(2) Esterification of vinylcarboxylic acid (2) (353 mg) with oxalyl chloride and benzyl alcohol in the presence of pyridine in a conventional manner gives vinyl ester (3) (305 mg).

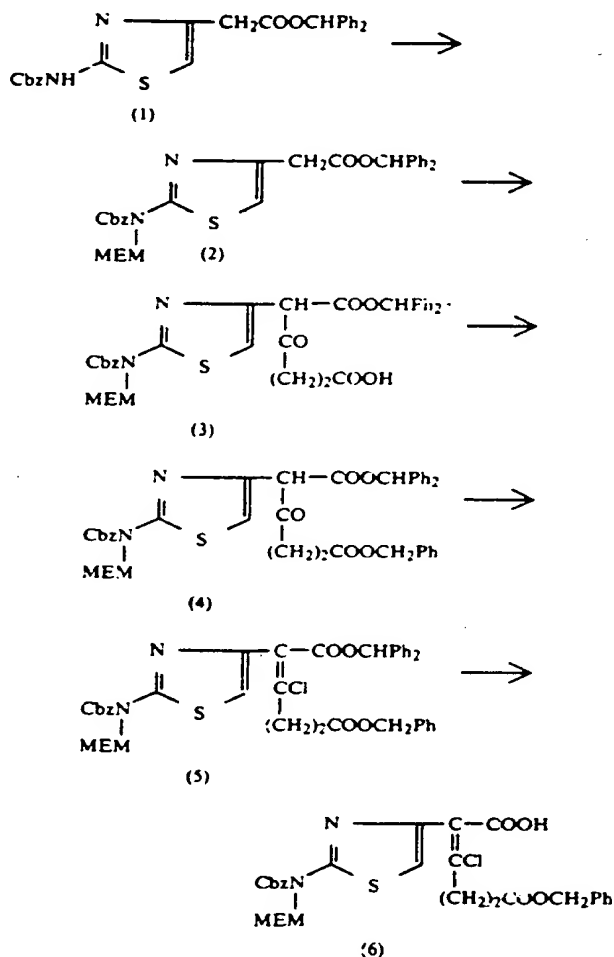
NMR (CDCl₃) δ : 1.85–3.00 (m, 6H), 5.07 (s, 2H), 5.25 (s, 2H), 6.48 (s, 1H), 7.05 (s, 1H), 7.10–7.55 (m, 20H) ppm.

(3) Stirring a mixture of vinyl ester (3) (275 mg), trifluoroacetic acid (0.5 ml), and anisole (1 ml) for 15 minutes at room temperature gives half ester (4) (95 mg).

NMR (CDCl₃+CD₃OD) δ : 1.80–3.00 (m, 6H), 5.09 (s, 2H), 5.26 (s, 2H), 6.25 (s, 1H), 7.05–8.00 (m, 10H) ppm.

Preparation A-9

2-[2-(N-Methoxyethoxymethyl-N-benzyloxycarbonylamino)thiazol-4-yl]-3-chloro-5-benzyloxycarbonyl-2-pentenoic acid (6)



(1) To a solution of aminoester (1) (115 mg) in N,N-dimethylformamide (1 ml) are added potassium carbonate (45 mg) and methoxyethoxymethyl chloride (0.043 ml). After stirring at room temperature for 1.5 hours, the mixture is diluted with iced hydrochloric acid and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated. The residue is purified

by silica gel chromatography to give methoxyethoxymethylamino ester (2). Yield: 74%.

NMR (CDCl₃) δ : 3.25 (s, 3H), 3.77 (s, 2H), 5.28 (s, 2H), 5.55 (s, 2H), 6.68 (s, 1H) ppm.

(2) To a solution of 0.3M-lithium bistrimethylsilylamide in tetrahydrofuran (1.4 ml) is added a solution of methoxyethoxymethylamino ester (2) (100 mg) in tetrahydrofuran (1 ml) at -78° C. under nitrogen. After stirring for 15 minutes, a solution of succinic anhydride (22 mg) in tetrahydrofuran (0.5 ml) is added to the solution. After 50 minutes' stirring at -78° C., the reaction mixture is acidified with 4N-hydrochloric acid (0.5 ml) and extracted with dichloromethane. The extract is washed with water, dried, and concentrated. The residue is purified by silica gel chromatography to give ketoester (3) (64%) and amino ester (1) (24%).

NMR (CDCl₃) δ : 3.27 (s, 3H), 5.32 (s, 2H), 5.50, 5.65 (2x s, 2H), 9.4 (brs, 1H) ppm.

(3) To a solution of keto ester (3) (541 mg) in benzene (5 ml) is added a 0.485M-solution (1.81 ml) of sodium methoxide in methanol. After stirring for 5 minutes, the mixture is concentrated. The residue is dissolved in N,N-dimethylformamide (5 ml), mixed with benzyl bromide (0.149 ml), stirred for 5.5 hours at room temperature, let stand overnight, and subjected to usual work-up and silica gel chromatography to afford ketodiester (4). Yield: 33%.

NMR (CDCl₃) δ : 3.26 (s, 3H), 5.05 (s, 2H), 5.32 (s, 2H), 5.55, 5.63 (2x s, 2H) ppm.

(4) To a solution of triphenylphosphine (284 mg) in tetrahydrofuran (4 ml) cooled at -15° C. are added a 0.85M solution of chlorine in carbon tetrachloride (1.27 ml), triethylamine (0.152 ml), and a solution of ketodiester (4) (160 mg) in tetrahydrofuran (2 ml). The mixture is warmed to room temperature, stirred for 6.5 hours, subjected to usual work-up, and silica gel chromatography to give chlorodiester (5). Yield: 67%.

This product is a mixture of cis and trans (1:1) geometric isomers.

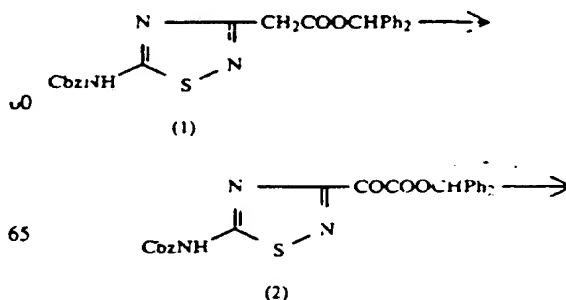
IR (CHCl₃) ν : 1720 cm⁻¹.

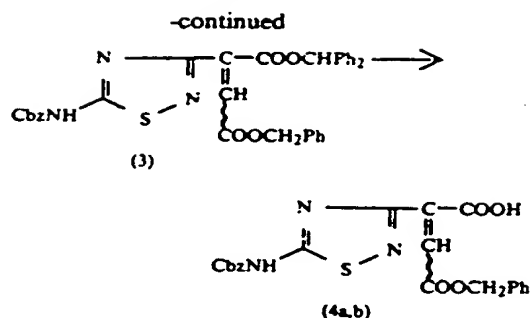
(5) To an ice cold solution of chlorodiester (5) (109 mg) in anisole (1 ml) is added trifluoroacetic acid (0.3 ml). After stirring at room temperature for 1 hour, the mixture is concentrated, and the residue is purified by silica gel chromatography to give chloromonoester (6) trifluoroacetate salt (112 mg). This product is a mixture of cis and trans (1:1) geometric isomers.

IR (CHCl₃) ν : 3350, 1720, 1680 cm⁻¹.

Preparation A-10

2-(5-Benzyloxycarbonylamino-1,2,4-thiadiazol-3-yl)-3-benzyloxycarbonyl-2-propenoic acid (4)





(1) To a solution of ester (1) (1.012 g) in dioxane (10 ml) is added selenium dioxide (0.66 g). After stirring for 2 hours at 100° C., the mixture is filtered. The filtrate is concentrated. The residue is dissolved in ether and purified by silica gel chromatography (eluting with a hexane-acetone (3:2) mixture) to give ketoester (2) (1.025 g). Yield: 98.3%.

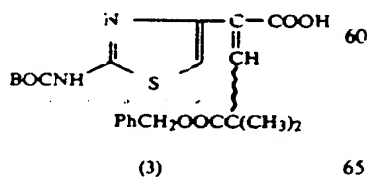
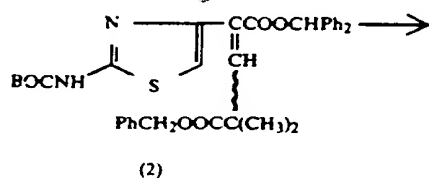
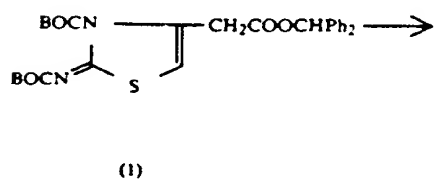
IR (Nujol) ν : 3380, 1720, 1240, 1085 cm^{-1} .

(2) A solution of ketoester (2) (1.025 g) and triphenylphosphoranimideneacetic acid benzyl ester (1.06 g) in dioxane (20 ml) is stirred at 100° C. for 2 hours and concentrated. The residue is purified by silica gel chromatography (eluting with acetone-hexane (3:1 to 3:2) mixture) to give diester (3) (1.24 g). Yield: 92%. mp. 173°-174° C.

(3) To a solution of diester (3) (348 mg) in dichloromethane (4.7 ml) are added anisole (0.35 ml) and trifluoroacetic acid (0.76 ml). After stirring for 1 hour at room temperature, the mixture is concentrated and washed with ether to give cis-monoester (4a) (147 mg). Yield: 58.3%. mp. 201°-202° C. The washing is concentrated, washed with hexane, and crystallized from a mixture of ether and hexane to give trans-monoester (4b) (98 mg). Yield: 38.9%. mp. 155°-156° C.

Preparation A-11

2-(2-t-Butoxycarbonylaminothiazol-4-yl)-4-methyl-4-benzyloxycarbonyl-2-pentenoic acid (3)



(1) To a solution of acetate (1) (628 mg) in tetrahydrofuran (16 ml) cooling at -50° C. is added potassium

t-butoxide (282 mg). After stirring for 5 minutes, the mixture is mixed with benzyl 2-formyl-2,2-dimethylacetate (0.32 ml), stirred for 20 minutes, warmed to room temperature in 5 minutes, neutralized with 10% hydrochloric acid, and extracted with ethyl acetate. The extract is washed with saline, dried, and concentrated. The residue is dissolved in benzene (10 ml), mixed with DBU (0.36 ml), stirred at room temperature for 4 hours, neutralized with 10% hydrochloric acid, washed with water, dried, concentrated, dissolved in benzene (10 ml), mixed with aqueous sodium sulfite (250 mg) solution (10 ml), and stirred for 24 hours. The benzene layer is washed with water, dried, concentrated, and purified by silica gel chromatography to give diester (2), cis isomer (431 mg; 59% yield) and trans isomer (158 mg; yield: 22%).

IR (CHCl_3) ν : 3410, 1725 cm^{-1} (cis isomer).

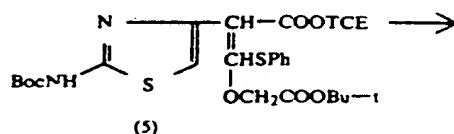
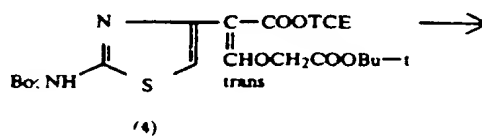
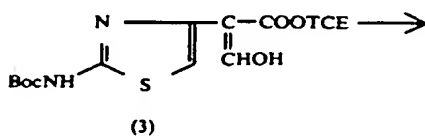
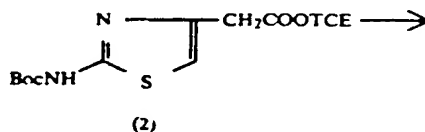
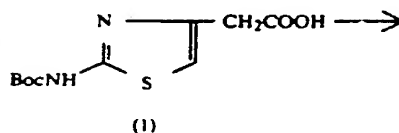
IR (CHCl_3) ν : 3400, 1720 cm^{-1} (trans isomer).

(2) To a solution of diester (2), cis isomer (431 mg), in dichloromethane (8 ml) is added a mixture of anisole (1.2 ml) and trifluoroacetic acid (1.2 ml). After stirring at 0° C. for 3 hours, the mixture is concentrated and purified by silica gel chromatography to give cis-isomer of monoester (3) (242 mg). Yield: 77%. mp. 158°-160° C. (decomp. recrystallized from benzene).

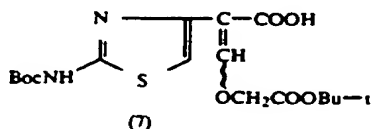
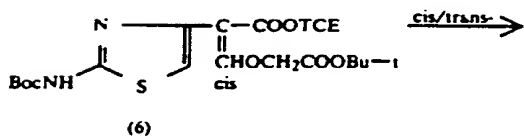
(3) To a solution of diester (2), trans isomer (237 mg), in dichloromethane (4 ml) is added a mixture of anisole (0.6 ml) and trifluoroacetic acid (0.6 ml). After stirring at 0° C. for 3.5 hours, the mixture is concentrated and purified by silica gel chromatography to give trans-isomer of monoester (3) (98 mg). Yield: 57%. mp. 175°-177° C. (decomp. recrystallized from benzene).

Preparation A-12

2-(2-t-Butoxycarbonylaminothiazol-4-yl)-3-t-butoxycarbonylmethoxy-2-propenoic acid (7)



-continued



(1) To a suspension of acetic acid (1) (11 g) in dichloromethane (120 ml) is added triethylamine (90 ml). The mixture is cooled at -78°C , mixed with 2,2,2-trichloroethyl chloroformate (4.87 ml) and *N,N*-dimethylaminopyridine (432 mg), stirred at 0°C for 10 minutes and at room temperature for 2 hours, diluted with ethyl acetate, washed with water, dried, and concentrated. The residue is purified by 10% aqueous silica gel chromatography (eluting with a benzene-ethyl acetate (9:1) mixture) to give trichloroethyl ester (2) (9.10 g). Yield: 66%.

IR (CHCl₃) ν : 3400, 1760, 1720, 1150 cm^{-1} .

(2) To a suspension of sodium hydride (2.88 g) in tetrahydrofuran (80 ml) is dropwise added a solution of trichloroethyl ester (2) (9.10 g) and 2,2,2-trichloroethyl formate (6.21 g) in tetrahydrofuran (34 ml). After stirring at room temperature for 2 hours, the mixture is diluted with ethyl acetate, acidified with acetic acid (5.3 ml), washed with water, dried, and concentrated. The residue is crystallized from petroleum ether to give formylester (3) (4.49 g). Yield: 46%.

IR (CHCl₃) ν : 3420, 1735, 1620 cm^{-1} .

(3) To an ice cold solution of formylester (3) (4.49 g) in *N,N*-dimethylformamide (40 ml) is added 60% sodium hydride (426 mg). The mixture is stirred until gas evolution ceases, mixed with *t*-butylbromoacetate (3.15 g), kept at room temperature overnight, diluted with ethyl acetate, washed with saline, dried, concentrated, and purified by silica gel chromatography (eluting with a benzene-ethyl acetate (19:1 to 2:1) mixture) to give diester (4) (3.03 g). Yield: 53%.

IR (CHCl₃) ν : 3400, 1723, 1630, 1150, 1120 cm^{-1} .

(4) To a solution of diester (4) (3.03 g) in tetrahydrofuran (30 ml) are added benzenethiol (0.70 ml) and triethylamine (0.79 ml). The mixture is stirred at room temperature for 3.5 hours, concentrated, and purified by silica gel chromatography (eluting with benzene-ethyl acetate (9:1 to 8:2) mixture) to give phenylthiopropionate (5) (3.36 g). Yield: 92%.

The product is 7:3 mixture of the two geometric isomers. IR (CHCl₃) ν : 3400, 1750, 1725, 1155, 1120 cm^{-1} .

(5) To a solution of phenylthiopropionate (5) (3.15 g) in dichloromethane (35 ml) cooled at -40°C is added *m*-chloroperbenzoic acid (80%, 1.07 g). The mixture is stirred at -40°C for 10 minutes and at room temperature for 10 minutes, diluted with ethyl acetate, stirred with aqueous 2% sodium hydrogen sulfite, and stirred at room temperature for 5 minutes. The organic layer is taken, washed with aqueous 5% sodium hydrogen carbonate and saturated saline, dried, concentrated, dissolved in benzene (150 ml), and refluxed for 15 minutes. The mixture is washed with aqueous 5% sodium hydrogen carbonate and saturated saline, dried, concentrated,

and purified by silica gel chromatography (eluting with a benzene-ethyl acetate (9:1 to 1:1) mixture) to give diester (6) (1.13 g). Yield: 45%.

5 IR (CHCl₃) ν : 3420, 1730, 1620, 1540, 1153, 1140 cm^{-1} .

(6) To a solution of diester (6) (0.80 g) in acetic acid (8 ml) is added zinc powder (2.0 g). After stirring at room temperature for 1 hour, the mixture is diluted with dichloromethane, mixed with 2*N*-hydrochloric acid, stirred for 10 minutes at room temperature, filtered to remove solid, and the organic layer is taken. This is washed with water, dried, and concentrated to give *Z*-isomer of monoester (7) (605 mg). Yield: 100%.

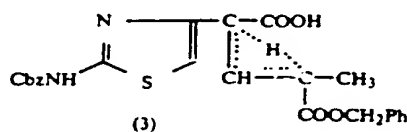
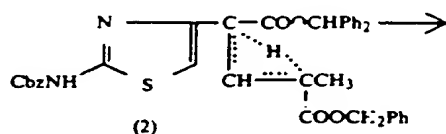
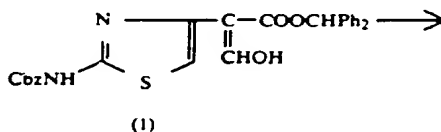
IR (CHCl₃) ν : 3400, 3550-2500, 1725, 1620, 1150 cm^{-1} .

20 *E*-isomer of monoester (7) (750 mg) is recovered from the mother liquor. Yield: 30%.

IR (KBr) ν : 3420, 1742, 1710, 1610, 1130 cm^{-1} .

Preparation A-13

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-4-benzyloxycarbonylpentenoic acid (3)



(1) A solution of hydroxymethylene (1) (1.46 g) and benzyloxycarbonyl ethylidenetriphenylphosphorane (2.5 g) in toluene (20 ml) is stirred at 80°C for 19 hours and at 110°C for 4 hours, and then concentrated. The residue is purified by silica gel chromatography to give diester (2) (0.808 g). Yield: 43%.

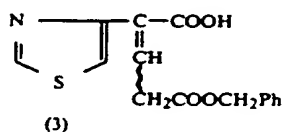
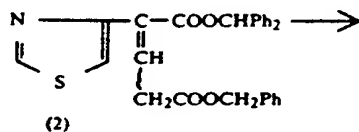
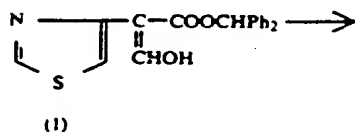
NMR (CDCl₃) δ : 1.15 (d, $J=7$ Hz, 1.5H), 1.71 (s, 1.5H), 4.90 (d, $J=9$ Hz, 0.5H) ppm.

(2) To a solution of diester (2) in dichloromethane (20 ml) are added anisole (3 ml) and trifluoroacetic acid (3 ml). After stirring at room temperature for 3 hours, the mixture is concentrated and triturated in a mixture of hexane and ether to give monoester (3) (508 mg). Yield: 85%.

IR (CHCl₃) ν : 3400, 1725 cm^{-1} .

31

Preparation A-14

2-(Thiazol-4-yl)-4-benzoyloxycarbonyl-2-butenic acid
(3)

(1) To a solution of formylester (1) (11.5 g) in benzene (220 ml) is added benzyloxycarbonylmethylidene phosphorane (19.5 g). After refluxing for 7 to 10 hours, the mixture is concentrated to a half to a third volume and purified by silica gel chromatography (eluting with a benzene-ethyl acetate (30:1) mixture) to give diester (2) (15.5 g). Yield: 97%. The product is a mixture of cis and trans geometric isomers.

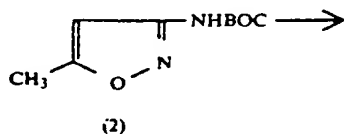
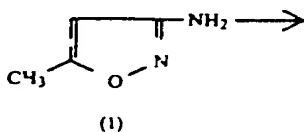
IR (CHCl₃): 1720 cm.

(2) To a solution of diester (2) (15.0 g) in dichloromethane (150 ml) is added trifluoroacetic acid (32 ml) at 0° C. After stirring at room temperature for 1.5 hours, the mixture is concentrated. The residue is stirred in hexane, diluted with ethyl acetate, and extracted with saturated aqueous sodium hydrogen carbonate. The extract is acidified with 10% hydrochloric acid to pH 3 to 4 and extracted with ethyl acetate. The extract is dried, concentrated, and triturated in a mixture of ether and hexane (1:1) to give monoester (3). Yield: 55%. This product is a mixture of cis and trans (1:1) geometric isomers.

NMR (CDCl₃-CD₃OD) δ: 3.53, 3.76 (d, J=8 Hz, 2H), 5.13, 5.15 (2x s, 2H), 7.23, 7.38 (2x t, J=8 Hz, 1H), 7.35 (s, 5H), 7.57, 7.61 (d, J=2 Hz, 1H), 8.79, 8.82 (d, J=2 Hz, 1H) ppm.

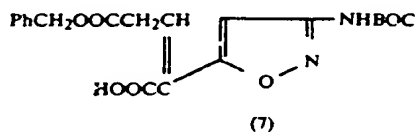
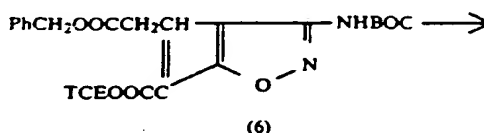
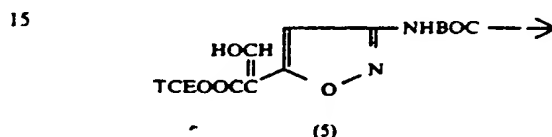
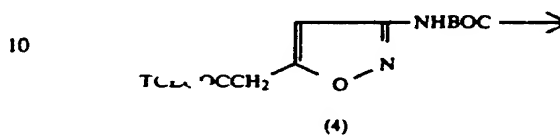
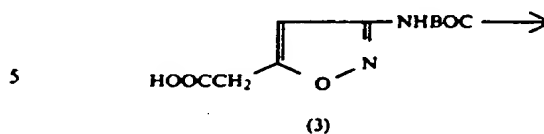
Preparation A-15

2-(3-t-Butoxycarbonylamino-5-isoxazolyl)-4-benzoyloxycarbonyl-2-butenic acid (7)



32

-continued



(1) A solution of 3-amino-5-methylisoxazole (1) (56 g) in di-*t*-butylpyrocarbonate is stirred at 105°-110° C. for 17 hours. The mixture is concentrated and diluted with ether and water. The organic layer is taken, washed with water, diluted hydrochloric acid, water, and saline, dried, and concentrated. The residue is washed with petroleum ether to give *t*-butoxycarbonylamine (2) (75 g). mp 108°-109° C.

(2) To a solution of diisopropylamine (23.4 ml) under nitrogen in tetrahydrofuran (90 ml) cooled at -20° C. is added *n*-butyllithium (1.6N-hexane solution 125 ml). After stirring for 15 minutes, the mixture is cooled to -78° C., mixed with a solution of *t*-butoxycarbonylamine (2) (8.3 g) in tetrahydrofuran (40 ml) over 2 minutes period, stirred for 1 hour, quenched with dry-ice (20 g), and concentrated. The residue is dissolved in water, washed with ether, acidified with hydrochloric acid under ice cooling, and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated. The residue is washed with ether to give acetic acid (3) (4.35 g). mp 173°-174° C. (decomp.).

(3) To a solution of acetic acid (3) in dichloromethane (200 ml) is added triethylamine (8.63 ml) at 0° C. This is cooled to -78° C., mixed with trichloroethyl chloroformate (13.1 g) and 4-dimethylaminopyridine (0.76 g), and stirred for 15 minutes. The mixture is warmed to room temperature, kept overnight, concentrated, diluted with water, and extracted with ethyl acetate. The extract is washed with diluted hydrochloric acid, aqueous sodium hydrogen carbonate, water, and saline, concentrated, and purified by silica gel chromatography (eluting with benzene-ethyl acetate (3:1) mixture) to give trichloroethyl ester (4) (19 g). mp 146°-147° C.

(4) To a suspension of 60% sodium hydride (6.72 g) in tetrahydrofuran (220 ml) at -30° to -10° C. is added a

solution of Trichloroethylester (4) and trichloroethyl formate (14.4 ml) in tetrahydrofuran (100 ml) over a 40 minutes period. After 1.5 hour's stirring, the mixture is poured into iced hydrochloric acid and extracted with ethyl acetate. The extract is washed with water and saline, dried, concentrated, and washed with petroleum ether to give hydroxymethylidene compound (5) (17.45 g). mp > 210° C.

(5) A solution of hydroxymethylidene compound (5) (8.06 g) and benzyloxycarbonylmethylidenetriphenylphosphorane (11.1 g) in dioxan (350 ml) is stirred at 55° C. for 9 hours. The mixture is concentrated, dissolved in water and ethyl acetate, washed with diluted hydrochloric acid, aqueous sodium hydrogen carbonate, water, and saline, dried, concentrated, and purified by silica gel chromatography (eluting with a mixture of benzene and ethyl acetate (1:0 to 15:1) to give diester (6) (6.35 g).

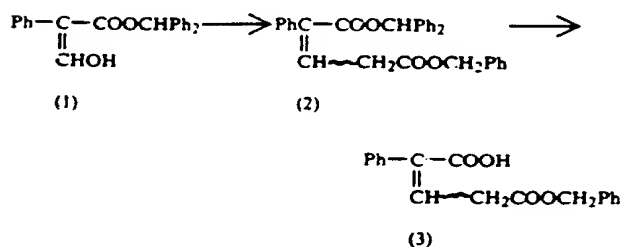
IR (CHCl₃) v: 3410, 2950, 1735, 1607, 1585 cm⁻¹.

(6) To a solution of diester (6) (1.85 g) in dichloromethane (20 ml) is added zinc (5 g) and acetic acid (20 ml) at 0° C. After 40 minutes stirring, the mixture is poured into dichloromethane and diluted hydrochloric acid, filtered to remove solid, and extracted with dichloromethane. The extract is washed with water and saline, dried, concentrated, and purified by silica gel chromatography (eluting with a benzene-ethyl acetate (3:1) mixture) to give monocarboxylic acid (7) (0.25 g).

IR (KBr) v: 3400, 3250, 2960, 1736, 1618 cm⁻¹.

Preparation A-16

2-Phenyl-4-benzyloxycarbonyl-2-butenic acid (3)



(1) To a solution of 2-formylphenylacetic acid diphenylmethyl ester (1) (1.94 g) in dioxane (20 ml) is added benzyloxycarbonylmethylidenetriphenylphosphorane (3.16 g) at room temperature. After stirring at 60° to 65° C. for 50 minutes, the mixture is concentrated and purified by silica gel chromatography (eluting with dichloromethane) to give diester (2) (1.81 g). Yield: 61%.

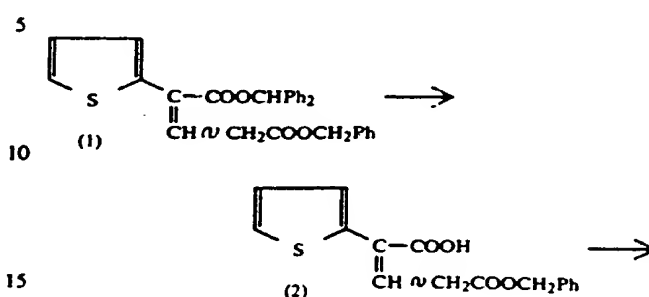
NMR (CDCl₃) δ: 3.18, 3.58 (2 × d, J = 8 Hz, 2H), 5.12, 5.24 (2 × s, 2H), 6.93 (s, 1H) ppm.

(2) To a solution of diester (2) (1.77 g) in dichloromethane (40 ml) are added anisole (4 ml) and trifluoroacetic acid (4 ml) at 0° C. After 2.5 hours' stirring, the mixture is concentrated and triturated in hexane to give monoester (3) (0.84 g). Yield: 73%. This is a mixture of cis and trans (17:83) geometric isomers.

IR (CHCl₃) v: 1730, 1690 cm⁻¹.

Preparation A-17

2-(2-Thienyl)-4-benzyloxycarbonyl-2-butenic acid (2)



Diester (1) (3.3 g) prepared in a manner similar to Preparation A-16 is dissolved in dichloromethane (60 ml), mixed with anisole (7 ml) and trifluoroacetic acid (7 ml) at 0° C., stirred for 2.5 hours, concentrated, and triturated in hexane. Resulting solid is purified by hexane-ether giving monoester (2) (1.19 g). Yield: 56%.

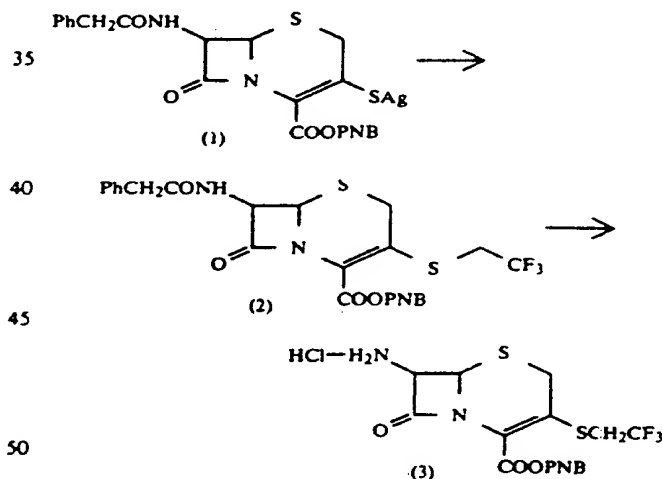
Diester (1): IR (CHCl₃) v: 1730 sh, 1722, 1165 cm⁻¹.

Monoester (2): IR (CHCl₃) v: 1730, 1695 cm⁻¹.

PREPARATION B (INTRODUCTION OF 3-SUBSTITUENTS)

Preparation B-1

7β-Amino-3-(2,2,2-trifluoroethylthio)-3-cephem-4-carboxylic acid p-nitrobenzyl ester (3)



(1) To a suspension of silver mercaptide (1) (1.86 g) in hexamethylphosphorotriamide (45 ml) is added sodium iodide (0.96 g). After stirring at room temperature for 50 minutes under nitrogen, the mixture is mixed with trifluoromethanesulfonic acid trifluoroethyl ester (2.95 g). After stirring at room temperature for 1 hour, the reaction mixture is poured into ice water and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture) to give sulfide (2) (1.03 g). mp. 159°-160° C.

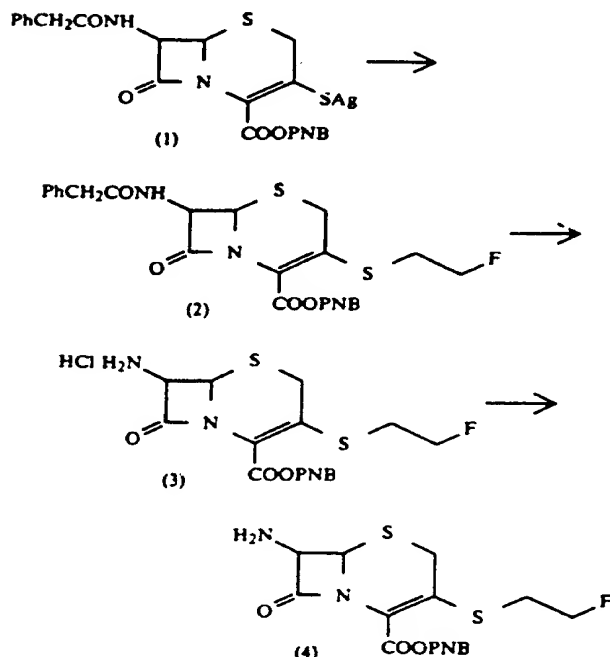
(2) To an ice cold solution of sulfide (2) (690 mg) in dichloromethane (22 ml) are added phosphorus pentachloride (675 mg) and pyridine (0.288 ml). After stirring at room temperature for 2 hours, the mixture is cooled

to -40°C ., diluted with methanol (22 ml), stirred at 0°C . for 2 hours, mixed with water (0.5 ml), and concentrated. The residue is triturated in ether to separate solid, which is suspended in dichloromethane, washed with aqueous sodium hydrogen carbonate and water, and concentrated to give amine (3) (562 mg).

IR (CHCl_3) ν : 3300 br, 1775, 1735 cm^{-1} .

Preparation B-2

7beta-Amino-3-(2-fluoroethylthio)-3-cephem-4-carboxylic acid p-nitrobenzyl ester (4)



(1) To a suspension of silver mercaptide (1) (2 g) in hexamethylphosphorotriamide (60 ml) are added p-toluenesulfonic acid 2-fluoroethyl ester (2.95 g) and sodium iodide (2.02 g). After keeping at room temperature for 4.5 hours, the mixture is poured into ice water (100 ml) and extracted with ethyl acetate. The extract is washed with water, dried, concentrated, dissolved in dichloromethane, and diluted with ether to separate thioether (2). mp. $144^{\circ}\text{--}149^{\circ}\text{C}$. Yield: 87.8%.

IR (CHCl_3) ν : 3400, 1780, 1720, 1680, 1630 cm^{-1} .

(2) To a solution of thioether (2) (1.54 g) in dichloromethane (38.5 ml) are added pyridine (0.52 ml) and phosphorus pentachloride (1.207 g). After keeping at room temperature for 2.5 hours, the reaction mixture is cooled to -40°C ., diluted with isobutanol (38.5 ml), kept at 0°C . for 3 hours, and filtered to collect separated crystals of amine hydrochloride (3). Yield: 91%.

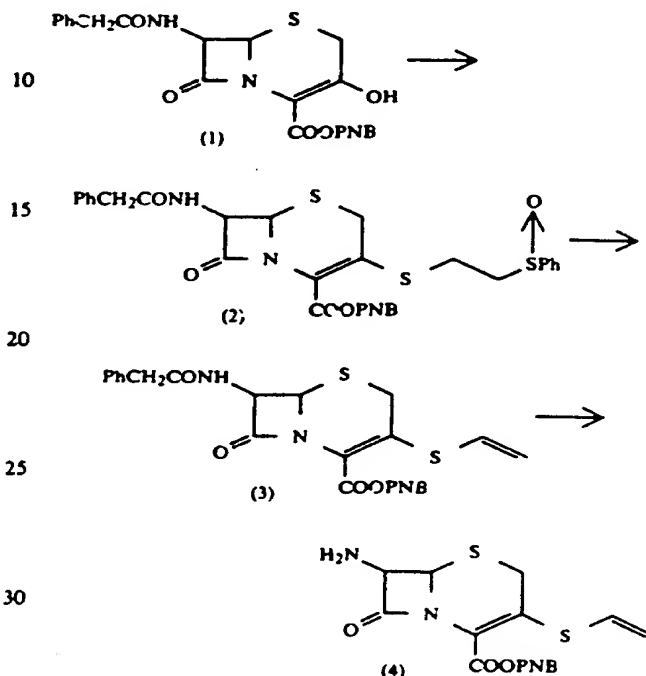
IR (Nujol) ν : 3140, 2645, 2585, 1773, 1604, 1600, 1512, 1492, 1460 cm^{-1} .

(3) A mixture of amine hydrochloride (3) (1.186 g), ethyl acetate (50 ml), sodium hydrogen carbonate (1.107 g), and water (30 ml) is stirred at 0°C . The organic layer is washed with aqueous sodium hydrogen carbonate and water, dried, and concentrated to give amine (4). Yield: 94.2%.

IR (CHCl_3) ν : 3400, 1772, 1726, 1602 1513 cm^{-1} .

Preparation B-3

7beta-Amino-3-vinylthio-3-cephem-4-carboxylic acid p-nitrobenzyl ester (4)



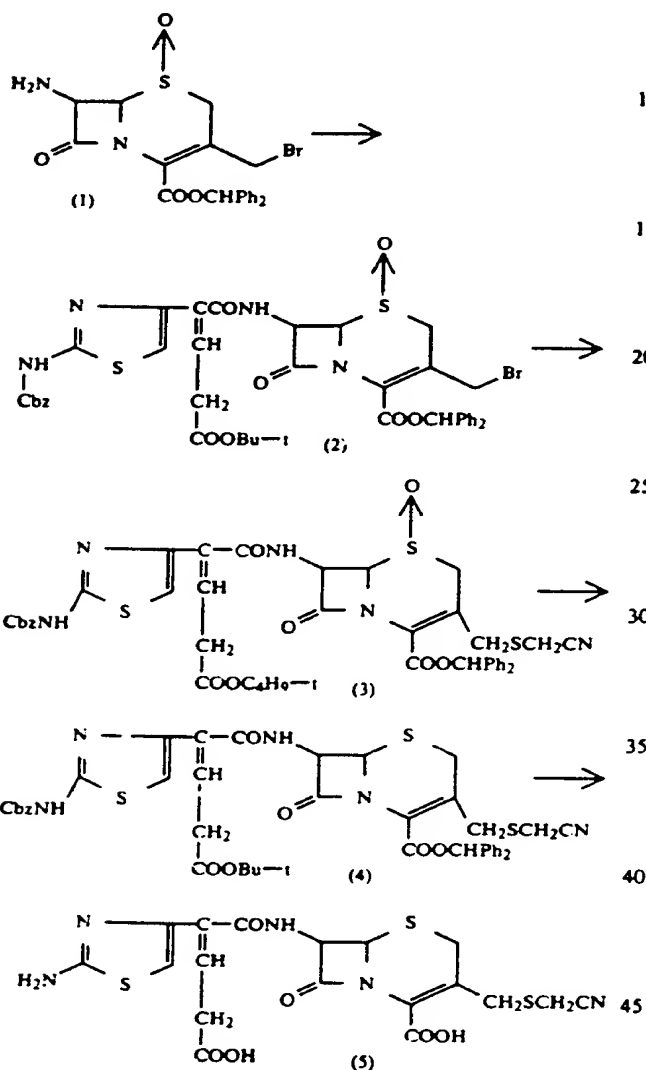
(1) To a solution of 3-enol (1) (9.38 g) in acetonitrile (120 ml) are added diphenyl chlorophosphinate (6.57 g) and diisopropylaminoethane (2.97 g). After stirring for 2 hours, this is mixed with 2-(benzenesulfonyl)ethanethiol (3.16 g), diisopropylaminoethane (2.19 g), and acetonitrile (6 ml), and stirred at -40°C . to -25°C . for 2.5 hours. The mixture is poured into iced hydrochloric acid and extracted with dichloromethane. The extract is washed with water, dried, and concentrated. The residue is crystallized from ethyl acetate-ether to give sulfoxide (2) (6.84 g). mp. $174^{\circ}\text{--}176^{\circ}\text{C}$.

(2) A solution of sulfoxide (2) (2 g) in 1,1,2-trichloroethane (40 ml) is refluxed for 11 hours under nitrogen. The reaction mixture is concentrated, and crystallized from ether to give vinyl thioether (3) (1.38 g). mp. $193^{\circ}\text{--}194^{\circ}\text{C}$.

(3) To a stirred and ice cold solution of vinyl thioether (3) (440 mg) in dichloromethane (15 ml) are added phosphorus pentachloride (358 mg) and pyridine (149 mg) under nitrogen. After stirring at room temperature for 2 hours, the reaction mixture is cooled to -40°C ., diluted with methanol (15 ml), and stirred for 2 hours at 0°C . The mixture is mixed with water (1 ml), concentrated, washed with ether, suspended in dichloromethane, and washed with aqueous 10% sodium hydrogen carbonate and water, dried, and concentrated. The residue is crystallized from a mixture of dichloromethane and ether to give amine (4) (204 mg). mp. $152^{\circ}\text{--}154^{\circ}\text{C}$.

Preparation B-4

7beta-[2-(2-Aminothiazol-4-yl)-4-carboxy-2-butenamido]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid (5)



(1) To a solution of bromomethyl compound (2) (340 mg) (prepared by amidating Amine (1) in a manner similar to Example 2) in *N,N*-dimethylformamide (3 ml) is added at -70°C . an ethanol solution of sodium cyanomethylmercaptide (prepared from cyanomethyl thiolacetate (71 mg) and sodium ethylate in ethanol). After 7 hours' stirring at -65°C . to -70°C ., the mixture is poured into ethyl acetate, washed with water, dried and concentrated. The residue is purified by silica gel chromatography (eluting with a mixture of benzene and ethyl acetate (3:1) to give oxide (3). Yield: 57.2%.

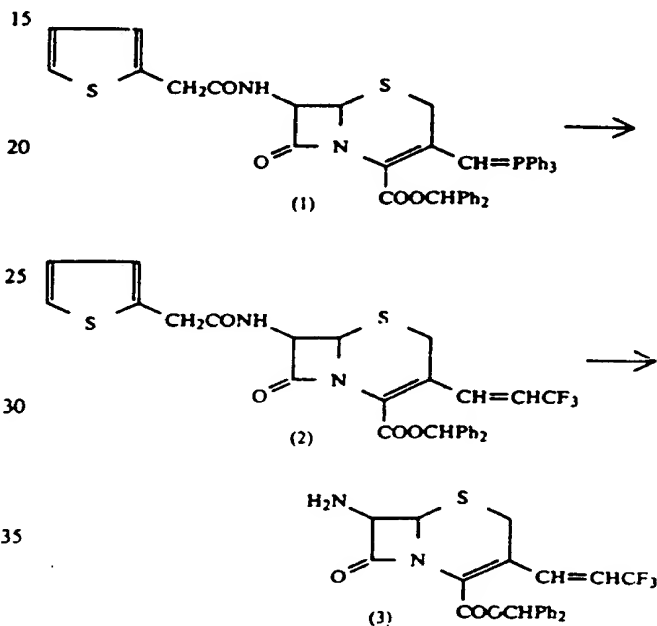
(2) To a solution of oxide (3) (690 mg) in acetone (10 ml) are added potassium iodide (883 mg) and acetyl chloride (0.339 ml) at -35°C . After 90 minutes' stirring at -20°C . to -25°C ., the mixture is diluted with ethyl acetate, washed with diluted sodium thiosulfate, and aqueous sodium hydrogen carbonate, dried, and concentrated to give sulfide (4). Yield: 85.6%.

(3) To a solution of sulfide (4) (550 mg) in anisole (10 ml) is added a solution of aluminum chloride (1.24 g) in

anisole (5 ml) at -30°C . After 3 hours' stirring, the mixture is diluted with hydrochloric acid and washed with ethyl acetate. The aqueous layer is purified with 5 synthetic adsorbent HP 20 (Mitsubishi Chemical K.K.) and eluted to give aminocarboxylic acid (5). Yield: 74.4%.

Preparation B-5

7beta-Amino-3-(3,3,3-trifluoro-1-propenyl)-3-cephem-4-carboxylic acid diphenylmethyl ester (3)



(1) Trifluoroacetaldehyde ethyl hemi ketal (4 ml) is added dropwise to phosphoric acid heating at 165°C . Evolving trifluoroacetaldehyde is condensed at -78°C . and dissolved in ethyl acetate (6 ml).

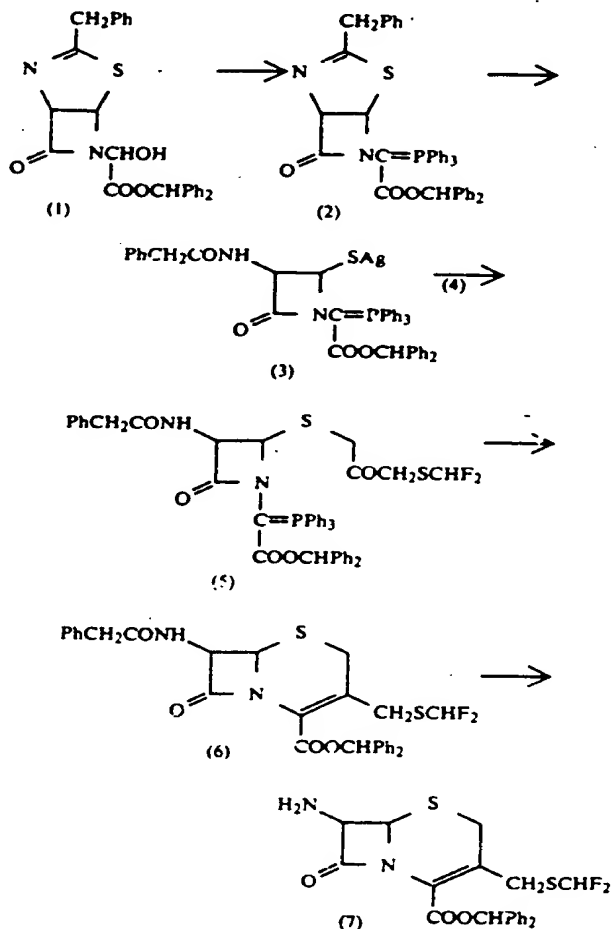
(2) To a suspension of phosphorane (1) (1.38 g) in a mixture (60 ml) of dichloromethane and ethyl acetate (5:1) cooled at -70°C . is added the solution prepared as in above (1). After stirring at -70°C . for 10 minutes and 30 minutes at room temperature, the mixture is concentrated. The residue is purified by silica gel chromatography (eluting with a mixture (9:1) of benzene and ethyl acetate) to give trifluoropropene (2). Yield: 91%.

IR (CHCl_3) ν : 3380, 1787, 1722, 1682 cm^{-1} .

(3) To a solution of trifluoropropene (2) (292 mg) in benzene (5 ml) are added pyridine (89 microliter) and phosphorus pentachloride (208 mg). After 2 hours' stirring at room temperature, the mixture is diluted with methanol (5 ml). After 15 minutes' stirring, the reaction mixture is diluted with ice-water, neutralized, and extracted with ethyl acetate. The extract is washed with water, dried, and concentrated to give amine (3). Yield: 65%.

Preparation B-6

7beta-Amino-3-difluoromethylthio-3-cephem-4-carboxylic acid diphenylmethyl ester (7)



(1) To a suspension of glycolate (1) (22.8 g) in dichloromethane (300 ml) are added pyridine (4.63 ml) and thionyl chloride (4 ml) at -20°C . to -23°C . over a 24 minutes period. After stirring for 10 minutes at -20°C . and for 30 minutes at 0°C ., the reaction mixture is washed with ice water and dried over magnesium sulfate. To the solution are added pyridine (4.63 ml) and triphenylphosphine (13 g). After stirring at room temperature for 2 hours and refluxing for 2 hours, the mixture is washed with water, and purified by silica gel chromatography (eluting with benzene-ethyl acetate

(2:1) mixture) to give phosphoranilidene ester (2) (20.13 g).

(2) To a solution of phosphoranilidene ester (2) (16.65 g) in dioxane (80 ml) are added a solution of 99% silver perchlorate monohydrate (5.87 g) in water (19 ml) and aqueous 60% perchloric acid (7.96 ml) at room temperature. After stirring for 1 hour, the mixture is diluted with dichloromethane and iced water. The organic layer is taken, washed with water, dried, and concentrated to give silver mercaptide (3).

(3) To a solution of silver mercaptide (3) in hexamethylphosphorotriamide (100 ml) are added 1-(difluoromethylthio)-3-chloroacetone (4) (3.95 g) and sodium iodide (3.55 g). After 2 hour stirring at room temperature, the reaction mixture is diluted with ethyl acetate and water. The organic layer is taken, washed with water, dried, and evaporated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (1:1) mixture) to give ketone (5).

Above 1-(difluoromethylthio)-3-chloroacetone (4) can be prepared as follows;



To a solution of diazomethane in ether (200 ml) prepared from N-nitrosomethylurea (20.6 g) is added dropwise a solution of difluoromethylthioacetyl chloride (10 g) in ether (20 ml) under ice cooling over 20 minutes period. After stirring at 0°C . for 20 minutes and at room temperature for 2 hours, the mixture is saturated with hydrogen chloride under ice cooling over 30 minutes. The reaction mixture is diluted with ice water, ether layer is taken, washed with water, dried, concentrated, and distilled to give (4) from fractions evaporating at bp (1 mmHg) $52^{\circ}\text{--}53^{\circ}\text{C}$. as colorless liquid.

(4) To a solution of ketone (5) (8.388 g) in toluene (200 ml) is added hydroquinone (180 mg) and refluxed for 14 hours. After evaporating toluene, the mixture is purified by silica gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture) to give cephem (6) (4.42 g).

NMR (CDCl_3) δ : 3.58 (s, 2H), 3.73 (s, 2H).

(5) To an ice cold solution of cephem (6) (4.42 g) in dichloromethane (80 ml) are added pyridine (1.35 ml) and phosphorus pentachloride (3.17 g). After stirring at 0°C . for 10 minutes and at room temperature for 90 minutes, the mixture is cooled to -45°C . to -55°C ., mixed with cold methanol (110 ml), stirred at 0°C . for 30 minutes, diluted with ice water, and neutralized. The organic layer is taken, washed with water, dried, and concentrated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture) to give amine (7) (2.686 g).

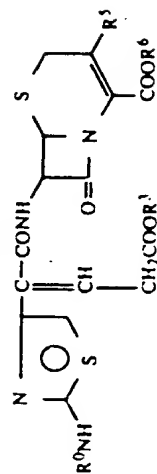
NMR (CDCl_3) δ : 1.73 (brs, 2H) ppm.

55

60

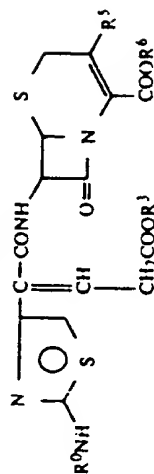
65

Esters



| No | cis:trans | R ⁰ | R ¹ | R ⁵ | R ⁶ | IR(CHCl ₃) ν: cm ⁻¹ | ¹ H NMR(CDCl ₃) δ: ppm | Example No. |
|----|-----------|----------------|---|----------------|----------------|--|---|--------------------------------------|
| 1 | | H | Me | H | H | nd | 3.70-4.30(m, 4H), 4.13, 4.16(2 x s, 3H), 5.56, 5.62(2 x d, J = 5Hz, 1H), 6.20, 6.26(2 x d, J = 5Hz, 1H), 6.66-6.83(m, 1H), 6.90, 7.26(2 x t, J = 9Hz, 1H), 7.06, 7.13(2 x s, 1H) [D ₂ O]. | (3-1) |
| 2 | cis | H | Me | H | BH | 1787, 1731, 1680, 1280. | 3.35-3.47(m, 2H), 3.58(d, J = 8Hz, 2H), 3.70(s, 3H), 4.98(d, J = 5Hz, 1H), 5.44(brs, 2H), 5.95, 6.04(dd, J ₁ = 5Hz, J ₂ = 9Hz, 1H), 6.47(s, 1H), 6.61(t, J = 8Hz, 1H), 6.56-6.66(m, 1H), 6.95(s, 1H), 7.24-7.48(m), 8.56(d, J = 9Hz, 1H). | (4-4) |
| 3 | trans | H | Me | H | BH | 1785, 1730, 1678, 1280. | 3.40(d, J = 8Hz, 2H), 3.35-3.47(m, 2H), 3.68(s, 3H), 4.92(d, J = 5Hz, 1H), 5.59(brs, 2H), 5.94, 6.03(dd, J ₁ = 5H, J ₂ = 9Hz, 1H), 6.48(s, 1H), 6.53-6.63(m, 1H), 6.90(s, 1H), 7.14(t, J = 8Hz, 1H), 7.23-7.45(m, 10H), 8.65(d, J = 9Hz, 1H). | (4-4) |
| 4 | cis | H | Bzl | H | H | 3270, 1770, 1735, 1722 [Nujol]. | 3.44(d, J = 7.5Hz, 2H), 3.54-3.67(m, 2H), 5.10(d, J = 5Hz, 1H), 5.17(s, 2H), 5.80, 5.89(dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 5.40(s, 1H), 6.42-6.59(m, 2H), 7.41(s, 3H), 9.39(d, J = 8Hz, 1H) [CD ₃ SOCD ₃]. | (3-1) |
| 5 | trans | H | Bzl | H | H | 3280, 1772, 1735, 1725 [Nujol]. | 3.54-3.69(m, 4H), 5.15(d, J = 5Hz, 1H), 5.15(s, 2H), 5.78, 5.80-dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 6.45-6.53(m, 1H), 6.66(s, 1H), 6.78(t, J = 5Hz, 1H), 7.40(s, 3H), 9.25(d, J = 8Hz, 1H) [CD ₃ SOCD ₃]. | (3-1) |
| 6 | cis | H | Bzl | H | BH | 1782, 1722, 1670, 1278. | 3.32-3.46(m, 2H), 3.62(d, J = 8Hz, 2H), 4.95(d, J = 5Hz, 1H), 5.13(s, 2H), 5.31(brs, 2H), 5.92, 6.02(dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 6.46(s, 1H), 6.53-6.61(m, 1H), 6.63(t, J = 8Hz, 1H), 6.94(s, 1H), 7.21-7.47(m), 8.67(d, J = 8Hz, 1H). | (4-3) |
| 7 | trans | H | Bzl | H | BH | 1780, 1721, 1670, 1280. | 3.30-3.45(m, 4H), 4.88(d, J = 5Hz, 1H), 5.11(s, 2H), 5.52(brs, 2H), 5.92, 6.02(dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 6.41(s, 1H), 6.50-6.65(m, 1H), 6.88(s, 1H), 7.15(t, J = 7.5Hz, 1H), 7.16-7.48(m), 8.61(d, J = 8Hz, 1H). | (4-3) |
| 8 | cis | Obz | H | H | BH | 1782, 1725, 1675, 1555 [Nujol]. | 3.56(d, J = 8Hz, 2H), 3.4-3.8(m, 2H), 5.04(d, J = 5Hz, 1H), 5.26(s, 2H), 5.90(d, J = 5Hz, 1H), 6.70(t, J = 8Hz, 1H), 6.60-6.75(m, 1H), 6.95(s, 1H), 6.95(s, 1H), 7.25-7.55(m, 15H) [CDCl ₃ -CD ₃ OD]. | (3-9) |
| 9 | trans | Obz | t-Bu | H | BH | 3330, 1775, 1725, 1670, 1630. | 1.34(s, 9H), 2.58-3.26(m, 4H), 4.70(s, 1H), 5.07, 5.51, ABq, J = 13Hz, 2H), 5.68, 5.76(dd, J = 5Hz, J = 8Hz, 1H), 6.30-6.39(m, 1H), 6.61(s, 1H), 6.75(s, 1H), 7.10-7.57(m, 15H), 7.67(d, J = 8Hz, 1H). | (2-1), (15) (3-1), (6-1), (3). |
| 10 | 15:85 | Obz | CH ₃ CH CH ₃ | H | BH | 3359, 1779, 1732, 1675, 1281, 1091. | nd | (2-17) |
| 11 | 1:1 | Obz | CHMe CH CH ₃ | H | BH | 3358, 1779, 1730, 1675, 1283, 1092. mp. 150-151° C. | 1.06(d, J = 7Hz, 1.5H), 1.18(d, J = 7Hz, 1.5H), 2.63-3.32(m, 4H), 4.66(d, J = 4.5Hz, 1H), 4.85-5.76(m, 6H), 6.31(m, 1H), 6.56(s, 1H), 6.68(s, 1/2H), 6.71(s, 1/2H). | (2-18) |

Eastern



| No | cis:trans | R ⁰ | R ¹ | R ² | R ³ | R ⁶ | IR(CHCl ₃) ν: cm ⁻¹ | ¹ H NMR(CDCl ₃) δ: ppm | Example No. |
|----|-----------|----------------|---|----------------|----------------|----------------|--|---|-------------------------|
| 12 | | Obz | CH ₂ CMe CH ₂ | | H | BH | 3345, 1780, 1735, 1679, 1287, 1092. | nd | (2-21) |
| 13 | 2:3 | Obz | CH ₂ CH CHMe | | H | BH | 3358, 1780, 1729, 1676, 1282, 1240, 1092. mp. 138 ~ 140° C. | 1.58(d, J = 6 Hz, 9/5H), 1.64(d, J = 6 Hz, 6/5H), 2.65 ~ 3.36(m, 4H), 4.38(d, J = 6 Hz, 2H), 4.69(d, J = 5 Hz, 1H), 5.06, 5.53(ABq, J = 12 Hz, 2H), 5.40 ~ 5.79(m, 3H), 6.28 ~ 6.39(m, 1H). | (2-18) |
| 14 | trans | Obz | CMe ₂ C=I CH ₂ | | H | BH | 3455, 1779, 1728, 1676, 1282, 1240, 1093. mp. 133 ~ 135° C. | 1.55(s, 3H), 1.61(s, 3H), 2.62 ~ 3.32(m, 4H), 4.52(d, J = 8.4z, 2H), 4.64(d, J = 4.5 Hz, 1H), 5.18(m, 1H), 5.02, 5.50(ABq, J = 12 Hz, 2H), 5.67(dd, J = 4.5 Hz, 8 Hz, 1H), 6.29(m, 1H), 6.58(s, 1H), 6.68(s, 1H). | (2-18) |
| 15 | trans | Obz | CH ₂ CH CMe ₂ | | H | BH | 3345, 1780, 1735, 1675, 1635. mp. 132 ~ 135° C. | 1.56(s, 3H), 1.62(s, 3H), 2.64 ~ 3.30(m, 4H), 4.45(bnd, J = 8 Hz, 2H), 4.67(d, J = 4.1z, 1H), 5.16(bnd, J = 8 Hz, 1H), 5.03, 5.50(ABq, J = 12 Hz, 2H), 5.65, 5.74(dd, J = 5 Hz, J = 8 Hz, 1H), 6.27 ~ 6.36(m, 1H), 6.58(s, 1H), 6.69(s, 1H), 7.13 ~ 7.43(m, 16H), 7.60(d, J = 8 Hz, 1H). | (2-20) |
| 16 | mixt. | Obz | CH ₂ CH CHPh | | H | BH | 3340, 1778, 1730, 1677, 1283, 1088. | nd | (2-17) |
| 17 | 1:4 | Obz | Bzl | | H | H | nd | 3.00 ~ 3.90(m, 4H), 4.96, 5.00(2 × d, J = 5 Hz, 1H), 5.13(s, 2H), 5.23(s, 2H), 5.73 ~ 5.88(m, 1H), 5.76, 5.86(dd, J ₁ = 5 Hz, J ₂ = 9 Hz, 1H), 6.50 ~ 6.60(m, 1H), 6.93(s, 1H), 7.11(s, J = 8 Hz, 1H), 7.33(s, 5H), 7.36(s, 5H) [CDCl ₃ - CD ₃ OD]. | (2-7), (14) (3-1) |
| 18 | | Obz | Bzl | | H | H | 3160, 1775, 1720, 1670, 1630. | 3.34 ~ 3.50(m, 4H), 4.95(d, J = 5 Hz, 1H), 5.13(s, 2H), 5.23(s, 2H), 5.50(d, J = 5 Hz, 1H), 6.48 ~ 6.60(m, 1H), 6.94(s, 1H), 7.03 ~ 7.40(m, 11H). | (2-7), (14) (3-1) |
| 19 | 1:4 | Obz | Bzl | | H | BH | 3340, 1775, 1725, 1670. | 3.04(s, 2H), 3.6 ~ 4.1(m, 2H), 4.58(d, J = 5 Hz, 1H), 4.8 ~ 5.6(m, 4H), 5.68 (d, J = 5 Hz, 1H), 6.25(m, 1H), 6.59, 6.67(2 × s, 1H), 6.63(s, 1H), 7.0 ~ 7.9 (m, 22H). | (2-1), (15) (21), (6-1) |
| 20 | trans | Obz | Bzl | | H | BH | 3830, 1780, 1725, 1675, 1630. mp. 131 ~ 133° C. | 2.68 ~ 3.36(m, 4H), 4.69(d, J = 5 Hz, 1H), 4.98(s, 2H), 5.03, 5.46(ABq, J = 12 Hz, 2H), 5.65, 5.74(dd, J = 5 Hz, J = 8 Hz, 1H), 6.29 ~ 6.40(m, 1H), 6.60(s, 1H), 6.64(s, 1H), 7.10 ~ 7.47(m, 15H), 7.63(d, J = 8 Hz, 1H). | (2-5), (21) (6-2), 7. |
| 21 | | Obz | MeBzl | | H | BH | 3340, 1775, 1725. | 2.30(s, 3H), 2.70 ~ 3.37(m, 4H), 4.71(d, J = 5 Hz, 1H), 4.95(d, 2H), 5.04, 5.04. | (2-7) |

TABLE I(1)-continued

Esters

| No | cis:trans | R ⁰ | R ¹ | R ² | R ³ | R ⁴ | IR(CHCl ₃) ν, cm ⁻¹ | NMR(CDCl ₃) δ, ppm | Example No. |
|----|-----------|---|----------------|---|----------------|----------------|--|--|-------------|
| 32 | cis | $\text{tBuSi} \begin{array}{c} \diagup \\ \text{CH} \\ \diagdown \end{array} \begin{array}{c} \text{Me} \\ \text{Me} \end{array}$ | Bzl | H | | BH | 3390, 1780, 1720, 1670, 1630 | 0.28(s, 6H), 0.94(s, 9H), 3.17-3.75(m, 2H), 3.66(d, J = 7.5Hz, 2H), 4.68(s, 1H), 4.99(d, J = 5Hz, 1H), 5.16(s, 2H), 6.00(dd, J ₁ = 5Hz, J ₂ = 9Hz, 1H), 6.50(s, 1H), 6.57-6.65(m, 1H), 6.68(t, J = 7.5Hz, 1H), 6.97(s, 1H), 7.1-7.6(m, 15H), 8.35(d, J = 9Hz, 1H). | (2-1) |
| 33 | 1:3 | Chz | Bzl | Me | | BH | 3320, 1765, 1725, 1675 | 2.00(s, 3H), 2.27, 2.77(ABq, J = 17Hz, 2H), 3.03 (AB part of ABX, J = 16Hz, 3/2H), 3.63(AB part of ABX, J = 16Hz, 1/2H), 4.77(d, J = 4Hz, 1H), 4.9-5.6(m, 5H), 6.61, 6.66(2 x s, 1H), 6.69, 6.75(2 x s, 1H), 6.9-7.5(m, 21H), 7.70-7.89(2 x d, J = 7Hz, 1H). | (2-5) |
| 34 | 1:2 | Chz | Bzl | CH=CHCl ₂ | | BH | 3330, 1770, 1725, 1675, 1620 | 2.70-3.94(m, 4H), 4.73, 4.79(2 x d, J = 4Hz, 1H), 4.90-5.30(m, 7H), 6.36-6.64(m, 2H), 6.90-7.50(m, 22H), 7.74, 7.97(2 x d, J = 7Hz, 1H). | (2-15) |
| 35 | 2:1 | Chz | Bzl | CH=CHCN(Z) | | BH | 3407, 3345, 2210, 1783, 1728, 1679, 1631 | 2.7-4.2(m, 4H), 4.85, 4.92(2 x d, J = 4.5Hz, 1H), 5.07(s, 2H), 5.13(s, 2H), 5.20, 5.39(2 x d, J = 12Hz, 1H), 5.70(m, 1H), 6.49, 6.76(2 x s, 1H), 6.63, 6.67(2 x s, 1H), 6.5-8.1(m, 23H). | (2-3) |
| 36 | 2:1 | Chz | Bzl | CH=CHCN(Z) | | H | 3168, 2193, 1785, 1726, 1672 [Nujol] | 3.50(m, 2H), 4.02(m, 2H), 5.13(d, J = 4.5Hz, 1H), 5.17(s, 2H), 5.28(s, 2H), 5.45(d, J = 12.5Hz, 1H), 5.90(d, J = 4.5Hz, 1H), 6.53, 7.07(2 x m, 1H), 6.98(s, 1H), 7.1-7.7(m, 11H) [CDCl ₃ -CD ₃ OD]. | (3-1) |
| 37 | | Chz | Fzl | CH=CHCOOH-Bu (E) | | BH | 3391, 1779, 1728, 1618 | 1.41(s, 9H), 2.3-4.2(m, 4H), 5.04, 5.08(2 x d, J = 4.5Hz, 1H), 5.10(s, 2H), 5.17(s, 2H), 5.67(2 x m, 1H), 5.94(d, J = 16Hz, 1H), 6.63, 6.69(2 x s, 1H), 6.72, 6.76(2 x s, 1H), 6.4-7.7(m, 17H), 7.86(d, J = 16Hz, 1H). | (2-7) |
| 38 | | Chz | Bzl | CH=CHCOOH-Bu (E) | | H | 3170, 1780, 1730, 1613, 1302, 1229 [Nujol] | 1.49(s, 9H), 3.3-4.2(m, 4H), 5.03, 5.07(2 x d, J = 4.5Hz, 1H), 5.14(s, 2H), 5.23(s, 2H), 5.82(2 x m, 1H), 5.96(d, J = 16Hz, 1H), 6.65(m, 0.5H), 6.91(s, 1H), 7.0-7.5(m, 10.5H), 7.86(d, J = 16Hz, 1H). | (3-1) |
| 39 | | Chz | Bzl | CH=CHCF ₃ (3E:2Z) | | BH | 3330, 1775, 1725, 1675, 1620 | 2.7-3.6(m, 4H), 4.75-4.95(m, 1H), 4.95-6.0(m, 6H), 6.4-6.8(m, 2H), 7.05-7.85(m, 23H). | (2-16) |
| 40 | | Chz | Bzl | CH=CHCF ₃ (Z) | | DH | 3325, 3390, 1775, 1725, 1672, 1625, nd | 2.7-3.8(m, 4H), 4.8-5.9(m, 7H), 6.55-6.85(m, 3H), 7.0-7.7(m, 22H). | (2-16) |
| 41 | 1:2 | Chz | Bzl | CH ₂ N ⁺ OC ₃ H ₅ Cl ⁻ | | H | | 3.16, 3.68(ABq, J = 18Hz, 2H), 3.51(d, J = 8Hz, 2H), 5.12(s, 2H), 5.28(s, 2H), 5.20(d, J = 5Hz, 1H), 5.82(d, J = 5Hz, 1H), 5.37, 5.76(ABq, J = 20Hz, 2H), 7.00, 7.15(2 x s, 1H), 7.35(s, 5H), 7.42(s, 5H), 6.8-7.5(m, 1H), 8.0-9.3(m, 3H) [CD ₃ OD-CD ₃ COCF ₃ -D ₂ O]. | (2-30) |
| 42 | cis | Chz | Bzl | CH ₂ OMe | | BH | 3390, 1780, 1728, 1675, 1304, 1168, 1092 | 3.16(s, 3H), 3.25(s, 2H), 3.54, 3.68(AB parts of ABX, J ₁ = 19.2Hz, J ₂ = 7Hz, 2H), 4.14, 4.28(ABq, J = 15.5Hz, 2H), 4.91(d, J = 4.5Hz, 1H), 5.12(s, 2H), 5.16, 5.34(ABq, J = 18Hz, 2H), 5.65(dd, J ₁ = 4.5Hz, J ₂ = 8.5Hz, 1H), 6.62 (t, J = 7Hz, 1H), 6.75(s, 1H), 6.79(s, 1H), 7.23-7.40(m, 21H), 8.10(d, J = 8.5Hz, 1H). | (2-9) |
| 43 | trans | Chz | Bzl | CH ₂ OMe | | BH | 3425, 1778, 1726, 1675, 1302, 1220, 1090 | 2.95, 3.19(AB parts of ABX, J ₁ = 17Hz, J ₂ = 8.1Hz, 2H), 3.14(s, 3H), 3.18(s, 2H), 4.09, 4.27(ABq, J = 13.5Hz, 1H), 4.80(d, J = 4.5Hz, 1H), 5.02(s, 2H), 5.09, 5.37(ABq, J = 12.6Hz, 2H), 5.40(dd, J ₁ = 4.5Hz, J ₂ = 7Hz, 1H), 6.57(s, 1H), 6.63(s, 1H), 7.10(t, J = 8.1Hz, 1H), 7.20-7.42(m, 21H), 7.74(d, J = 7Hz, 1H). | (2-9) |

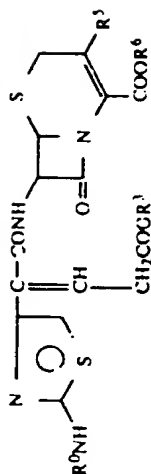


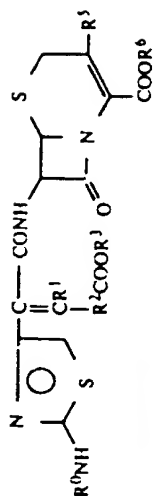
TABLE I(I)-continued

Esters

| No | cis:trans | R ⁰ | R ¹ | R ² | R ³ | R ⁴ | IR(CHCl ₃) ν, cm ⁻¹ | ¹ HMR(CDCl ₃) δ, ppm | Example No. |
|----|-----------|----------------|----------------|------------------------------------|-----------------|----------------|--|---|-------------|
| 54 | 1:1 | Cbz | Bzl | | | BH | 3385, 3170, 1779, 1723, 1673, 1620, 1560. | 3.38(d, J = 8 Hz, 2H), 3.51(overline{s}, 2H), 4.06(overline{s}, 2H), 4.23(overline{s}, 2H), 4.98, 5.01(2 × d, J = 4 Hz, 1H), 5.11(s, 2H), 5.20(s, 2H), 5.78(d, J = 4 Hz, 1H), 6.87 (s, 1H), 6.90(s, 1H), 7.00 ~ 7.60(m, 22H) [CDCl ₃ -CD ₃ OD(10:1)]. | (2-15) |
| 55 | cis | Cbz | Bzl | | | BH | 3400, 1785, 1725, 1670. | 3.40(s, 2H), 3.61(d, J = 7 Hz, 2H), 3.73(s, 3H), 4.11, 4.43(ABq, J = 14 Hz, 2H) 4.91(d, J = 5 Hz, 1H), 5.11(s, 2H), 5.14, 5.24(ABq, J = 12 Hz, 2H), 5.65(ddd, J ₁ = 5 Hz, J ₂ = 5 Hz, 1H), 6.62(t, J = 7 Hz, 1H), 6.78(s, 1H), 6.81(s, 1H), 7.1 ~ 7.6(m, 20H), 8.27(d, J = 8 Hz, 1H). | (2-29) |
| 56 | trans | Cbz | Bzl | | | BH | 1785, 1730, 1675. | 2.98(d, J = 8 Hz, 2H), 3.23(s, 2H), 3.75(s, 3H), 3.98, 4.52(ABq, J = 14 Hz, 2H), 4.80(d, J = 5 Hz, 1H), 5.06(s, 2H), 5.10(s, 2H), 5.40(ddd, J ₁ = 5 Hz, J ₂ = 6 Hz, 1H), 6.52(s, 1H), 6.77(s, 1H), 7.08(t, J = 8 Hz, 1H), 7.1 ~ 7.6(m, 20H), 7.77(d, J = 6 Hz, 1H). | (2-29) |
| 57 | | Cbz | Pzl | OMe | | BH | 3325, 1760, 1715, 1670, 1625. | 1.98, 2.69(ABq, J = 16 Hz, 2H), 2.76 ~ 4.01(m, 2H), 3.52(s, 3H), 4.92 ~ 5.34(m, 6H), 6.66(s, 1H), 6.88(s, 1H), 7.01 ~ 7.50(m, 21H). | (2-15) |
| 58 | | Cbz | Bzl | OSO ₂ Me | | BH | 3340, 1785, 1735, 1675, 1630. | 2.65 ~ 3.75(m, 2H), 2.94(s, 3H), 3.51(overline{s}, 2H), 4.86(d, J = 5 Hz, 1H), 5.03 (s, 2H), 5.02, 5.49(ABq, J = 13 Hz, 2H), 5.61, 5.70(s, 2H), 5.02, 5.49(ABq, J = 13 Hz, 2H), 5.61, 5.70(ddd, J ₁ = 5 Hz, J ₂ = 8 Hz, 1H), 6.50, 6.53, 6.60(3 × s, 2H). | (2-12) |
| 59 | 1:2 | Cbz | Bzl | Cl | | BH | 3350, 1785, 1740, 1685, 1635. | 2.64 ~ 3.95(m, 2H), 3.37(overline{s}, 2H), 4.78, 4.80(2 × d, J = 6 Hz, 1H), 4.94 ~ 5.13 (m, 2H), 5.00, 5.10(2 × s, 2H), 5.38(ddd, J ₁ = 8 Hz, J ₂ = 6 Hz, 1H), 6.55 ~ 6.67, 6.95 ~ 7.50(2 × m, 23H). | (2-28) |
| 60 | | BOC | Bzl | Cl | 2-Cephem isomer | PNB | 1778, 1745, 1727, 1675, 1350, 1150. | 1.52(s, 9H), 3.38(d, J = 8 Hz, 2H), 4.89(d, J = 2 Hz, 1H), 5.13(s, 2H), 5.28 (d, J = 4 Hz, 1H), 5.31(s, 2H), 5.43, 5.51(ddd, J ₁ = 4 Hz, J ₂ = 7 Hz, 1H), 6.35(d, J = 2 Hz, 1H), 6.93(s, 1H), 7.18(t, J = 8 Hz, 1H), 7.33(s, 5H), 7.52(d, J = 8 Hz, 2H), 8.20(d, J = 7 Hz, 1H), 8.23(d, J = 8 Hz, 2H), 8.99(overline{s}, 1H). | (2-24) |
| 61 | | MeCbz | MeBzl | SCH ₂ CH ₂ F | | PNB | 3350, 1780, 1732, 1676, 1620, 1606. | 2.32(s, 6H), 2.7 ~ 3.3(m, 4H), 3.39(s, 2H), 4.49(ddd, J ₁ = 4 Hz, J ₂ = 6 Hz, 2H), 4.82(d, J = 4 Hz, 1H), 5.02(s, 2H), 4.68, 5.48(ABq, J = 19 Hz, 2H), 5.21(s, 2H), 6.83(s, 1H), 7.0 ~ 7.3(m, 9H), 7.46(d, J = 9 Hz, 1H), 7.67(d, 8 Hz, 1H), 8.14(d, J = 9 Hz, 2H). | (2-17) |
| 62 | | MeCbz | MeBzl | SCH ₂ CH ₂ F | | BH | 3345, 1757, 1730, 1672, 1630, 1557, 1528. | 2.26(s, 6H), 2.1 ~ 2.7(m, 2H), 2.7 ~ 3.3(m, 4H), 4.31(ddd, J ₁ = 6 Hz, J ₂ = 4 Hz, 2H), 4.8 ~ 4.5(m, 6H), 6.65(s, 1H), 6.80(s, 1H), 7.0 ~ 7.7(m, 21H). | (2-5) |
| 63 | 1:1 | Cbz | Bzl | SCH ₂ CF ₃ | | PNB | 3330, 1775, 1725, 1665. | 2.8 ~ 3.7(m, 6H), 4.75 ~ 5.35(m, 8H), 6.82(s, 1H), 7.0 ~ 7.7(m, 12H), 7.45, 8.15(ABq, J = 9 Hz, 4H). | (2-22) |
| 64 | | Cbz | Bzl | SCH ₂ CF ₃ | | H | 3170(overline{s}, 1775, 1725, 1670. | nd | (3-1) |

TABLE I (2)

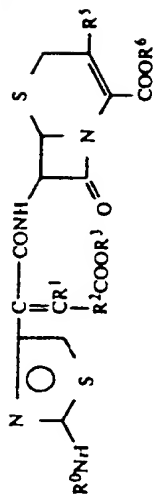
Esters



| No | cis:trans | R ⁰ | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | IR(CHCl ₃), ν _{cm} ⁻¹ | NMR(CDCl ₃), δ, ppm | Example No. |
|----|-----------|----------------|----------------|---------------------------------|----------------|-----------------------|-----------------------|----------------|---|---|-------------|
| 1 | cis | Obz | H | — | Bzl | Me | CH=CH ₂ | BH | 3400, 1765, 1720, 1680. | 1.96(s, 3H), 2.60, 3.68(Abq, J=18Hz, 2H), 4.88(d, J=4.5Hz, 1H), 5.07(s, 2H), 5.13, 5.27(Abq, J=12Hz, 2H), 5.86(dd, J ₁ =4.5Hz, J ₂ =7Hz, 1H), 6.59(s, 1H), 6.86(s, 1H), 7.01(s, 1H), 7.0~7.6(m, 20H), 8.21(d, J=7Hz, 1H). | (2-28) |
| 2 | cis | Obz | H | — | Bzl | CH=CH ₂ | CH=CH ₂ | BH | 3400, 1770, 1725, 1685. | 3.06, 3.18(Abq, J=18Hz, 2H), 4.95(d, J=5Hz, 1H), 4.9~5.4(m, 6H), 5.93(dd, J ₁ =5Hz, J ₂ =7.5Hz, 1H), 6.60(s, 1H), 6.89(s, 1H), 7.00(s, 1H), 6.85~7.6(m, 21H), 8.21(d, J=7.5Hz, 1H), 10.09(brs, 1H). | (2-23) |
| 3 | cis | Obz | H | — | Bzl | CH ₂ OCOMe | CH ₂ OCOMe | BH | 1770, 1725, 1680. | 1.98(s, 3H), 2.88, 3.28(Abq, J=19Hz, 2H), 4.52~5.22(m, 7H), 5.93(d, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.60(s, 1H), 6.88(s, 1H), 7.02(s, 1H), 7.0~7.6(m, 20H), 8.00(d, J=8Hz, 1H). | (2-17) |
| 4 | trans | Obz | H | — | Bzl | CH ₂ OCOMe | CH ₂ OCOMe | BH | 1780, 1735, 1675. | 1.97(s, 3H), 3.18(brs, 1H), 4.55(d, J=5Hz, 1H), 4.52~5.57(m, 7H), 6.70(s, 1H), 6.98(s, 1H), 7.1~7.6(m, 20H), 7.90(d, J=7.5Hz, 1H). | (2-17) |
| 5 | cis | Obz | H | CH ₂ CH ₂ | Bzl | H | H | BH | 3350, 1770, 1720, 1660, 1620, 1550, 1390, 1270. | 2.55(m, 4H), 3.30(m, 2H), 4.85(d, J=6.0Hz, 1H), 5.06(s, 4H), 5.90(m, 1H), 6.40(m, 1H), 6.63(s, 1H), 6.81(s, 1H), 7.30(m, 21H). | (2-20) |
| 6 | trans | Obz | H | CH ₂ CH ₂ | Bzl | H | H | BH | 3350, 1770, 1720, 1660, 1620, 1720, 1390, 1270. | 2.30(m, 4H), 3.08(m, 2H), 4.63(d, J=6.0Hz, 1H), 5.00(s, 4H), 5.70(m, 1H), 6.29(m, 1H), 6.53(s, 1H), 6.56(s, 1H), 6.98(s, 1H), 7.30(m, 21H). | (2-20) |
| 7 | | Obz | H | >CHMe | Bzl | H | H | BH | 3330, 1770, 1725, 1670. | 0.9~1.52(x d, 3H), 3.0~3.3(m, 2H), 3.4~4.5(m, 1H). | (2-21) |
| 8 | exo | Obz | H | >CHMe | Bzl | H | H | BH | 3370, 1785, 1725, 1690ah. | 1.74, 1.79, 1.90, 2.00(x 4 x s, 3H), 3.1~3.4(m, 2H). | (2-21) |
| 9 | cis | Obz | H | (CH ₂) ₃ | Bzl | H | H | BH | 3325, 2900, 1770, 1720, 1660, 1620, 1520, 1400, 1280. | 1.75(m, 2H), 2.30(m, 4H), 3.25(m, 2H), 4.80(d, J=6.0Hz, 1H), 5.08(s, 4H), 5.75(m, 1H), 6.32(m, 1H), 6.61(s, 1H), 6.78(s, 1H), 6.90(m, 1H), 7.30(m, 21H). | (2-21) |
| 10 | trans | Obz | H | (CH ₂) ₃ | Bzl | H | H | BH | 3325, 2910, 1770, 1720, 1660, 1620, 1520, 1400, 1280. | 1.70(m, 2H), 2.22(m, 4H), 3.11(m, 2H), 4.65(d, J=6Hz, 1H), 5.02(s, 4H), 5.70(m, 1H), 6.30(m, 1H), 6.48(s, 1H), 6.60(s, 1H), 7.00(m, 1H), 7.30(m, 21H). | (2-21) |
| 11 | cis | BOC | H | >CMe ₂ | Bzl | H | H | BH | 3390, 1780, 1720, 1665. | 1.52(s, 15H), 3.1~3.7(m, 2H), 4.91(d, J=5Hz, 1H), 5.13(s, 2H), 5.87(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.45(s, 1H), 6.54~6.64(m, 1H), 6.82(s, 1H), 6.94(s, 1H), 7.1~7.5(m, 15H). | (2-6) |
| 12 | trans | BOC | H | >CMe ₂ | Bzl | H | H | BH | 3400, 3340, 1780, 1720, 1665. | 1.34(s, 3H), 1.36(s, 3H), 1.52(s, 9H), 3.09(d, J=4Hz, 2H), 4.50, 4.78(Abq, J=12Hz, 2H), 4.67(d, J=5Hz, 1H), 5.62(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.32(s, 1H), 6.51(s, 1H), 6.61(s, 1H), 7.11(s, 1H), 7.1~7.5(m, 15H). | (2-6) |
| 13 | 3:2 | Obz | Cl | — | Bzl | H | H | BH | 3400, 1780, 1720. | nd | (2-1) |
| 14 | 1:1 | Obz N-MEM | Cl | CH ₂ CH ₂ | Bzl | H | H | BH | 3390, 1785, 1715, 1670. | 2.6~3.0(m, 2H), 3.25(s, 3H), 3.0~3.6(m, 4H), 3.55~3.85(m, 2H), 4.97, 5.02(2 x d, J=4.5Hz, 1H), 5.09, 5.11(2 x s, 2H), 5.33(s, 2H), 5.55, 5.67(2 x s, 2H), 5.8~6.2(m, 1H), 6.55~6.75(m, 1H), 6.68, 7.03(2 x s, 1H), 6.95(s, 1H), 7.15~7.6(m, 21H). | (2-16) |
| 15 | | Obz | Cl | (CH ₂) ₃ | Bzl | H | H | BH | 1785, 1725. | 1.70~2.90(m, 6H), 3.25~3.50(m, 2H), 4.87(d, J=5Hz, 1H), 5.00(s, 1H). | (2-21) |

TABLE I (2)-continued

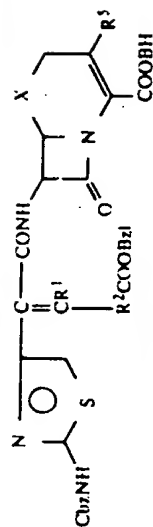
Esters



| No | cis:trans | R ⁰ | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | IR(CHCl ₃), ν -cm ⁻¹ | NMR(CDCl ₃), δ -ppm | Example No. |
|----|-----------|----------------|----------------|-------------------|----------------|----------------|----------------|----------------|---|--|-------------|
| 16 | | Obz | Cl | SClH ₂ | Bzl | BH | H | nd | | 2H), 5.23(s, 2H), 5.95(dd, J ₁ =5Hz, J ₂ =9Hz, 1H), 6.53(t, J=4Hz, 1H), 6.71(s, 1H), 6.82(s, 1H), 7.0-7.5(m, 20H), 3.23(m, 2H), 3.60(s, 2H), 4.80(d, J=5Hz, 1H), 5.03(s, 2H), 5.07, 5.90(A Bq, J=12Hz, 2H), 5.83(dd, J ₁ =5Hz, J ₂ =9Hz, 1H), 6.35(t, J=4Hz, 1H), 6.77(s, 1H), 6.90(s, 1H), 7.0-7.6(m, 20H). | (2-21) |

TABLE I (3)

Esters



| No | cis:trans | X | R ¹ | R ² | R ³ | IR (CHCl ₃) ν: cm ⁻¹ | NMR (CDCl ₃) δ: ppm | Example No. |
|----|-----------|-----------------|----------------|-----------------|------------------------------------|---|---|---------------|
| 1 | cis | SO ₂ | H | CH ₃ | H | 1795, 1725, 1670. | 3.1-4.12(m, 2H), 3.57(d, J=7Hz, 2H), 4.54(d, J=5Hz, 1H), 5.07(s, 2H), 5.18(s, 2H), 5.61(dd, J ₁ =5Hz, J ₂ =7Hz, 1H), 6.3-6.4(m, 1H), 6.60(t, J=7Hz, 1H), 6.85(s, 1H), 6.88(s, 1H), 7.1-7.5(m, 20H), 8.53(d, J=7Hz, 1H). | (2-20) |
| 2 | trans | SO ₂ | H | CH ₃ | H | nd | 2.9-4.15(m, 4H), 4.45(d, J=5Hz, 1H), 5.06(s, 2H), 5.10, 5.30(ABq, J=12Hz, 2H), 5.47(dd, J ₁ =5Hz, J ₂ =7Hz, 1H), 6.2-6.4(m, 1H), 6.77(s, 1H), 6.82(s, 1H), 7.11(t, J=8Hz, 1H), 7.1-7.5(m, 20H), 8.03(d, J=7Hz, 1H). | (2-20) |
| 3 | trans | SO ₂ | H | CH ₃ | H | 1800, 1720, 1670. | 3.0-3.9(m, 2H), 3.37(d, J=7Hz, 2H), 4.36(d, J=5Hz, 1H), 5.10(s, 2H), 5.18(s, 2H), 6.16(dd, J ₁ =5Hz, J ₂ =9Hz, 1H), 6.3-6.4(m, 1H), 6.84(s, 1H), 6.92(s, 1H), 7.1-7.5(m, 21H), 9.50(brs, 1H), 9.56(d, J=9Hz, 1H). | (2-20) |
| 4 | | SO | H | CH ₃ | CH ₃ CH ₂ CN | 3200, 2245, 1800, 1720, 1672, 1615, 1550. | 2.81(s, 2H), 3.34(d, J=7Hz, 2H), 3.60(s, 2H), 3.79(ABq, J=17Hz, 2H), 4.32(d, J=5Hz, 1H), 5.08(s, 2H), 5.14(s, 2H), 6.15(dd, J ₁ =5Hz, J ₂ =10Hz, 1H), 6.78(s, 1H), 6.94(s, 1H), 7.1-7.5(m, 20H), 9.54(d, J=10Hz, 1H), 9.67(brs, 1H). | (2-11) B-4 |
| 5 | 1:1 | SO | H | CH ₃ | H | 1800, 1722, 1668. | 2.79(s, 3H), 2.30(s, 3H), 3.27, 3.80(ABq, J=18Hz, 2H), 3.31, 3.40(2 x d, J=8Hz, 2H), 4.00(brs, 2H), 4.50(d, J=5Hz, 1H), 5.07, 5.11(2 x s, 4H), 6.08, 6.19(dd, J ₁ =10Hz, J ₂ =5Hz, 1H), 6.81(s, 1H), 6.83(s, 1H), 6.97-7.43(m, 19H), 8.33(s, 1H), 5.43(brs, 1H), 9.71(d, J=10Hz, 1H). | (2-11) |
| 6 | | S=O | H | CH ₃ | OH | 1800, 1730, 1640, 1615. | 3.30-3.80(m, 4H), 4.66(d, J=5Hz, 1H), 5.14(s, 2H), 5.23(s, 2H), 5.91(d, J=5Hz, 1H), 6.84(s, 1H), 6.88(s, 1H), 7.10-7.70(m) [CDCl ₃ -CD ₃ OD]. | (2-10) |
| 7 | 1:1 | O | H | CH ₃ | OMe | 3380, 3150, 1765, 1710, 1675. | 2.80-3.90(m, 2H), 3.30, 3.47(2 x s, 3H), 4.0-5.5(m, 9H), 6.4-6.85(m, 3H), 7.1-7.7(m), 8.13, 8.36(2 x s, 1H). | (2-15) |
| 8 | 1:1 | O | H | CH ₃ | OMe | 1770, 1720, 1685. | 2.1-4.0(m, 2H), 3.30, 3.40(2 x s, 3H), 3.74, 3.78(2 x s, 3H), 4.1-5.2(m, 9H), 6.18, 6.46(2 x s, 1H), 6.61(t, J=7Hz, 0.5H), 6.80, 6.83(2 x s, 1H), 7.0-7.6(m, 20.5H), 7.89, 8.24(2 x s, 1H). | (2-15) |

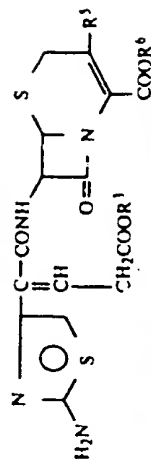
TABLE 1 (4)

Esters

| No | cis:trans | R | R ² | R ³ | IR(CHCl ₃) ν -cm ⁻¹ | ¹ H NMR(CDCl ₃) δ -ppm | Example No. |
|----|-----------|---------|-----------------|----------------|--|---|-------------|
| 1 | 1:1 | Ph | CH ₂ | H | 3390, 1790, 1730, 1680, 1630 | 3.06, 3.37(2 x d, J = 8Hz, 2H), 3.20-3.70(m, 2H), 4.92(d, J = 5Hz, 1H), 5.10, 5.14 (2 x s, 2H), 5.96(d, J = 5Hz, 1H), 6.56-6.63(m, 1H), 6.92(s, 1H), 7.10-7.45(m). | (2-26) |
| 2 | trans | | CH ₂ | H | 3390, 1785, 1725, 1675, 1630, 1495 | 3.23(d, J = 8Hz, 2H), 3.15-3.75(m, 2H), 4.94(d, J = 5Hz, 1H), 5.12(s, 2H), 5.88, 5.98(dd, J ₂ = 5Hz, J ₂ = 10Hz, 1H), 6.36(d, J = 10Hz, 1H), 6.52-6.63(m, 1H), 6.92-7.50(m, 2H). | (2-28) |
| 3 | 1:4 | | CH ₂ | | 3380, 1795, 1720, 1675, 1620 | 3.21, 3.54(2 x d, J = 8Hz, 2H), 3.68(s, 2H), 3.80(s, 3H), 4.22-4.35(ABq, J = 15Hz, 2H), 4.96(d, J = 5Hz, 1H), 5.11, 5.13(2 x s, 2H), 5.86, 5.96(dd, J ₁ = 5Hz, J ₂ = 9Hz, 1H), 6.34(d, J = 9Hz, 1H), 6.90-7.46(m, 2H). | (2-28) |
| 4 | 5:4 | BOC-NH- | CH ₂ | H | 3405, 1785, 1730, 1682, 1635 | 1.49(s, 9H), 3.10-3.75(m, 2H), 4.95, 4.97(2 x d, J = 4.5Hz, 1H), 5.93(dd, J ₁ = 9Hz, J ₂ = 4.5Hz, 1H), 5.14(s, 2H), 6.50-6.75(m, 1H), 6.85, 6.97(2 x s, 1H), 6.95(s, 1H), 7.10-7.80(m, 17H). | (2-10) |
| 5 | 1:1 | | CH ₂ | H | 1790, 1725, 1680, 1630 | 3.37, 3.72(2 x d, J = 8Hz, 2H), 3.03-3.80(m, 2H), 4.96(d, J = 5Hz, 1H), 5.13(s, 2H), 5.95, 6.04(dd, J ₁ = 5Hz, J ₂ = 9Hz, 1H), 6.55-6.66(m, 1H), 6.83(t, J = 8Hz, 0.5H), 6.95(s, 1H), 7.20-7.50(m, 16.5H), 8.52(d, J = 9Hz, 1H), 8.75, 8.84(d, J = 2Hz, 1H). | (2-7) |
| 6 | trans | | CH ₂ | H | 1780, 1720, 1670, 1620, 1515, 1340 | 3.13-3.73(m, 2H), 3.50(d, J = 7.5Hz, 2H), 5.02(d, J = 5Hz, 1H), 5.17(s, 2H), 5.99 (dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 6.57-6.68(m, 1H), 6.79(s, 1H), 7.2-7.6(m, 17H), 8.07, 8.21(ABq, J = 9Hz, 4H), 8.71(d, J = 8Hz, 1H), 9.20(s, 1H). | (2-17) |
| 7 | cis | | CH ₂ | H | 1780, 1720, 1665, 1625, 1515, 1340 | 3.13-3.75(m, 2H), 3.77(d, J = 7Hz, 2H), 5.03(d, J = 5Hz, 1H), 5.18(s, 2H), 5.98 (dd, J ₁ = 5Hz, J ₂ = 8Hz, 1H), 6.60-6.70(m, 1H), 6.92(t, J = 8Hz, 1H), 7.01(s, 1H), 7.2-7.6(m, 16H), 8.09, 8.23(ABq, J = 8Hz, 4H), 8.83(d, J = 8Hz, 1H), 9.21(s, 1H). | (2-27) |
| 8 | 1:1 | | CH ₂ | H | 1780, 1730, 1540, 1280 | 3.91-3.31(m, 1H), 3.64, 3.50(ABq, J = 10Hz, 1H), 3.67, 3.81(2 x d, J = 7Hz, 2H), 4.71, 4.84(2 x d, J = 5Hz, 1H), 5.04, 5.11(2 x s, 1H), 5.22, 5.29(ABq, J = 12Hz, 1H), 5.22(m, 1H), 5.6-6.1(m, 0.5H), 6.3-6.7(m, 1H), 6.22, 6.87(2 x s, 1H), 7.2-7.7(m, 23H), 8.33, 9.07(2 x d, J = 8Hz, 1H). | (2-1) |
| 9 | cis | | - | H | 3200, 1770, 1730, 1690, 1550, 1290 | 2.78-3.24(m, 2H), 4.88(d, J = 5Hz, 1H), 5.11(s, 2H), 5.17, 5.32(ABq, J = 13Hz, 2H), 6.09, 6.19(dd, J ₁ = 8Hz, J ₂ = 5Hz, 1H), 6.52(m, 1H), 6.86(s, 1H), 7.01(s, 1H), 7.27(m, 20H), 8.46(d, J = 8Hz, 1H). | (2-1) |

TABLE 2 (I)

Carboxylic acids



| No | cis:trans | R ¹ R ² | R ³ | IR ν, cm ⁻¹ | NMR δ, ppm | Example No. |
|----|-----------|--|----------------|--|---|---------------------------|
| 1 | 1:1 | H H | H | 1763, 1705, 1630 [KBr] | 3.22(d, J=7Hz, 1H), 3.4(d, J=7Hz, 1H), 3.60(s, 2H), 5.07, 5.11(2 x d, J=5Hz, 1H), 5.81(d, J=5Hz, 1H), 6.31, 6.57(2 x s, 1H), 6.3-6.8(m, 2H) [CD ₃ COCD ₃ -CD ₃ OD-D ₂ O] | (3-1), (4-1) |
| 2 | cas | H H (HCl salt) | H | 3425, 3300, 3260, 1760, 1715, 1657, 1620, 1548 [Nujol] | 3.31(d, J=7Hz, 2H), 3.51-3.63(m, 2H), 5.21(d, J=5Hz, 1H), 5.79(d, J=5Hz, 1H), 6.54-6.83(m, 2H), 6.63(s, 1H) [CD ₃ SOCd ₃ -CD ₃ OD] | (3-1), (2), (4-1), (2), 9 |
| 3 | cis | H H | H | 3380, 3260, 1770, 1700, 1650, 1572, 1546, 1362 [Nujol] | 3.68(d, J=8Hz, 2H), 3.9(A part of ABX, J ₁ =5.5Hz, J ₂ =20Hz, 1H), 4.13(B part of ABX, J ₁ =3.5Hz, J ₂ =20Hz, 1H), 5.65(d, J=5Hz, 1H), 6.30(d, J=5Hz, 1H), 6.78(X part of ABX, J ₁ =3.5Hz, J ₂ =5.5Hz, 1H), 6.95(s, 1H), 7.05(s, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-1), (4-1), 8 |
| 4 | 1:1 | H Me | H | 1760, 1710, 1630 [KBr] | 2.13(s, 3H), 3.39(d, J=7Hz, 2H), 5.03(d, J=4.5Hz, 1H), 5.08(d, J=4Hz, 1H), 5.73(d, J=4.5Hz), 5.76(d, J=4Hz, 1H), 6.43, 6.54(2 x s, 1H), 6.61, 6.94(2 x t, 7Hz, 1H) [CD ₃ SOCd ₃ -CD ₃ OD-CDCl ₃] | (1-4), (3-2), (4-2) |
| 5 | 1:1 | H CH=CH ₂ | H | 3280, 1760, 1630 [Nujol] | 3.66(d, J=8Hz, 2H), 4.10(m, 2H), 5.62-5.96(m, 3H), 6.16, 6.22(2 x d, J=4Hz, 1H), 6.85-7.46(m, 3H) [D ₂ O] | (1-4), (3-2), (4-2) |
| 6 | 1:1 | H CH=CHCN (Z) | H | 3195, 2205, 1764, 1611 [Nujol] | 3.3-4.2(m, 4H), 5.08, 5.15(2 x d, J=4.5Hz, 1H), 5.26(d, J=12Hz, 1H), 5.61, 5.71(2 x d, J=4.5Hz, 1H), 6.35, 6.43(2 x s, 1H), 6.53, 6.78(m, 1H), 6.98(d, J=12Hz, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 7 | 1:1 | H CH=CHCOOH (E) | H | 3267, 1770, 1612, [Nujol] | 2.8-3.4(m, 2H), 3.42, 3.72(ABq, J=14.5Hz, 2H), 5.10, 5.15(2 x d, J=4.5Hz, 1H), 6.3, 5.69(2 x d, J=1.5Hz, 1H), 5.90(d, J=16Hz, 1H), 6.36, 6.76(2 x m, 1H), 6.45, 6.53(2 x s, 1H), 7.23(d, J=16Hz, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 8 | 1:1 | H CH=CHCF ₃ (1Z, 2E) | H | 3340, 1770, 1708, 1640, 1530 [KBr] | 3.67(d, J=7.8Hz, 2H), 3.75-4.3(m, 2H), 5.67, 5.73(2 x d, J=4.5Hz, 1H), 6.15-6.70(m, 2H), 6.96, 7.24(2 x t, 7.8Hz, 1H), 7.05, 7.13(2 x s, 1H), 7.20, 7.68(2 x d, J=10Hz, J=16.5Hz, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 9 | 1:1 | H CH=CHCF ₃ (Z) | H | 3360, 1772, 1708, 1655, 1628, 1532 [KBr] | 3.68(d, J=7.8Hz, 2H), 3.99, 4.19(ABq, J=18Hz, 2H), 5.18, 5.73(2 x d, J=4.5Hz, 1H), 6.17, 6.27(2 x d, J=4.5Hz, 1H), 6.1-6.7(m, 1H), 7.05, 7.34(2 x t, 7.8Hz, 1H), 7.07, 7.15(2 x s, 1H), 7.23(d, J=12.8Hz, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 10 | 1:2 | H CH ₂ N ⁺ C ₃ H ₇ | Θ | 3380, 1770, 1620, 1525 [KBr] | 3.66, 4.08(ABq, J=18Hz, 2H), 3.78(d, J=8Hz, 2H), 5.66, 5.71(2 x d, J=5Hz, 1H), 5.80, 6.00(ABq, J=15Hz, 2H), 6.20, 6.26(2 x d, J=5Hz, 1H), 7.11, 7.24(2 x s, 1H), 6.8-7.5(m, 1H), 8.4-9.5(m, 5H) [D ₂ O] | (3-7), (4-2) |
| 11 | 2:3 | H CH ₂ OMe | H | 3170br, 1760, 1622 [Nujol] | nd | (1-4), (3-2), (4-2) |
| 12 | 3:5 | H CH ₂ OCOMe | H | 3275, 1770, 1720, 1630 [Nujol] | 2.75(s, 3H), 3.70(d, J=8Hz, 2H), 3.86, 4.13(ABq, J=18Hz, 2H), 5.60, 5.70(2 x d, J=6Hz, 1H), 6.22, 6.28(2 x d, J=6Hz, 1H), 6.98, 7.38(2 x t, J=8Hz, 1H), 7.07, 7.16(2 x s, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 13 | 2:3 | H CH ₂ OCONH ₂ | H | 3350, 1760, 1720, 1700 [Nujol] | 3.66(d, J=8Hz, 2H), 3.83, 4.08(ABq, J=18Hz, 2H), 5.12, 5.31(ABq, J=12Hz, 2H), 5.61, 5.67(2 x d, J=4Hz, 1H), 6.19, 6.24(2 x d, J=4Hz, 1H), 7.00, 7.14(2 x s, 1H), 6.95, 7.36(2 x t, J=8Hz, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 14 | 1:1 | Na CH ₂ SMc | Na | 3370, 1755, 1590, 1525 [KBr] | 2.46(s, 3H), 3.67(d, J=8Hz, 2H), 3.7-4.3(m, 4H), 5.62(d, J=5Hz, 1H), 5.66(d, J=4Hz, 1H), 6.12(d, J=5Hz, 1H), 6.17(d, J=4Hz, 1H), 6.94, 7.25(2 x t, J=8Hz, 1H), 7.05, 7.14(2 x s, 1H) [D ₂ O] | (1-2), (3-2), (4-2) |
| 15 | | H CH ₂ SCH ₂ CN | H | 3300, 2240, 1765, 1625, 1530 [Nujol] | 3.68(d, J=8Hz, 2H), 3.91, 4.20(ABq, J=13Hz, 2H), 4.01(s, 2H), 4.20(s, 2H), 5.65, 5.71(2 x d, J=5Hz, 1H), 6.19, 6.23(2 x d, J=5Hz, 1H), 6.97, 7.38(2 x t, J=8Hz, 1H), 7.07, 7.15(2 x s, 1H) [NaHCO ₃ -D ₂ O] | (1-4), (3-2), (4-2) |
| 16 | | H CH ₂ SCHF ₂ | H | 3275br, 1765, 1660 sh, 1625 [Nujol] | nd | (1-4), (3-2), (4-2) |

TABLE 2 (I)-continued

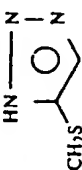

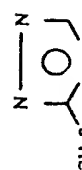
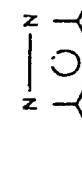
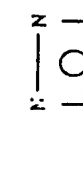
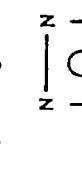
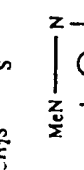
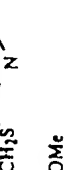

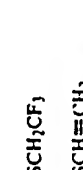


| | | | | | | |
|----|-----|--------------------------------------|---|---|--|----------------------|
| 17 | 2:3 | Na |  | Na 1748 [Nujol]. | 3.67(d, J=8Hz, 2H), 3.65-4.37(m, 2H), 4.50, 4.71(ABq, J=21Hz, 2H), 5.54, 5.59(2 x d, J=4.5Hz, 1H), 6.09, 6.15(2 x d, J=4.5Hz, 1H), 6.95, 7.35(2 x t, J=8Hz, 1H), 7.04, 7.14 (2 x s, 1H), 8.41(s, 1H) [D ₂ O]. | (1-1), (3-2), (4-2). |
| 18 | 3:5 | Na |  | Na 1770, 1662, 1630 [KBr]. | 3.60, 3.69(2 x d, J=7Hz, 2H), 3.91-4.10(m, 2H), 4.17-4.41(m, 2H), 5.04, 5.61(2 x d, J=5Hz, 1H), 6.10, 6.17(2 x d, J=5Hz, 1H), 6.93, 7.33(2 x t, J=7Hz, 1H), 7.03, 7.12(2 x s, 1H), 9.15(s, 1H) [Na-salt-D ₂ O]. | (1-1), (3-2), (4-2). |
| 19 | 1:1 | H |  | H 3300, 1764, 1627, 1529, 1367 [KBr]. | 3.69(d, J=8Hz, 2H), 4.07(ABq, J=17Hz, 2H), 4.75(ABq, J=12Hz, 2H), 5.58, 5.62(2 x d, J=4Hz, 1H), 6.18, 6.20(2 x d, J=4Hz, 1H), 6.98, 7.40(2 x t, J=8Hz, 1H), 7.03, 7.13(2 x s, 1H), 9.88(s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 20 | 1:1 | H |  | H 3390, 1763, 1622, 1523, 1376 [KBr]. | 3.18(s, 3H), 3.68(d, J=8Hz, 2H), 4.03(ABq, J=17Hz, 2H), 4.67(ABq, J=14Hz, 2H), 5.57, 5.61(2 x d, J=4Hz, 1H), 6.14, 6.17(2 x d, J=4Hz, 1H), 6.94, 7.37(2 x t, J=8Hz, 1H), 7.01, 7.11(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 21 | 1:1 | H |  | H 3300, 1763, 1621, 1511, 1382, 1355 [KBr]. | 3.69(d, J=8Hz, 2H), 4.16(ABq, J=18Hz, 2H), 4.53(ABq, J=13.5Hz, 2H), 5.58, 5.62(2 x d, J=4Hz, 1H), 6.14, 6.19(2 x d, J=4Hz, 1H), 6.97, 7.38(2 x t, J=8Hz, 1H), 7.04, 7.13(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 22 | 1:1 | H |  | H 3410, 1762, 1615, 1528, 1361 [KBr]. | 3.68(d, J=8Hz, 2H), 4.06(ABq, J=18Hz, 2H), 4.65(ABq, J=14Hz, 2H), 4.87, 5.01(2 x s, 2H), 5.58, 5.62(2 x d, J=4Hz, 1H), 6.14, 6.19(2 x d, J=4Hz, 1H), 6.70-7.50(m, 1H), 7.04, 7.13(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 23 | 1:1 | H |  | H 1745, 1710, 1630 [KBr]. | 3.37(d, J=8Hz, 2H), 3.69(s, 2H), 3.95(s, 3H), 4.35(s, 2H), 5.03, 5.07(2 x d, J=5Hz, 1H), 5.82(d, J=5Hz, 1H), 6.41, 6.53(2 x s, 1H), 6.61, 6.93(2 x t, J=8Hz, 1H) [CD ₃ SOCD ₃ -CD ₃ OD-CDCl ₃]. | (1-4), (3-6). |
| 24 | 3:5 | H OMe |  | H 3275, 1760, 1620 [Nujol]. | 3.68, 3.72(2 x d, J=8Hz, 2H), 3.73-4.25(m, 2H), 4.21, 4.23(2 x s, 3H), 5.64, 5.70(2 x d, J=6Hz, 1H), 6.00, 6.05(2 x d, J=6Hz, 1H), 6.97, 7.37(2 x t, J=8Hz, 1H), 7.10, 7.16(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 25 | 3:5 | H Cl |  | H 3275, 1760, 1621 [Nujol]. | 3.64, 3.65(2 x d, J=8Hz, 1H), 3.97, 4.34(4.00, 4.37(2 x ABq, J=18Hz, 2H), 5.68, 5.71(2 x d, J=6Hz, 1H), 6.17, 6.22(2 x d, J=6Hz, 1H), 6.94, 7.33(2 x t, J=8Hz, 1H), 7.03, 7.13(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-2), (4-2). |
| 26 | 1:2 | H SCH ₂ CH ₂ F |  | H 3300, 1763, 1660, 1629, 1531 [KBr]. | 3.52(d, J ₁ =22.5Hz, J ₂ =6Hz, 2H), 3.67(d, J=7.5Hz, 2H), 3.83, 4.41(ABq, J=17.1Hz, 2H), 5.07(d, J ₁ =47.7Hz, J ₂ =6Hz, 2H), 5.63, 5.69(2 x d, J=5Hz, 1H), 6.15, 6.21(2 x d, J=5Hz, 1H), 6.96, 7.36(2 x t, J=7.5Hz, 1H), 7.06, 7.15(2 x s, 1H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-4), (3-5). |
| 27 | 3:7 | Na SCH ₂ CF ₃ |  | Na nd | 3.70(d, J=7Hz, 2H), 3.6-4.4(m, 2H), 4.30, 4.85(ABq, J=15Hz, 2H), 5.67, 5.74(2 x d, J=4Hz, 1H), 6.20, 6.27(2 x d, J=4Hz, 1H), 7.00, 7.38(2 x t, J=7Hz, 1H), 7.07, 7.17(2 x s, 1H) [D ₂ O]. | (3-2), (4), (1-2). |
| 28 | 4:5 | H SCH=CH ₂ |  | H 1150, 1740, 1705 [Nujol]. | 3.68(d, J=7Hz, 2H), 4.15(bra, 2H), 5.6-6.2(m, 1H), 6.35(q, J ₁ =16Hz, J ₂ =8Hz, 1H), 6.8-7.6(m, 2H) [NaHCO ₃ -D ₂ O]. | (1-4), (3-4). |

TABLE 2 (2)

| Carboxylic acids | | | | | | | | | |
|------------------|-----------|----------------|---------------------------------|----------------|-----------------------|----------------|----------------|--|--|
| No | cis/trans | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | IR (KBr) ν : cm ⁻¹ | NMR δ : ppm |
| 1 | cis | H | — | H | Me | H | H | nd | 2.17(s, 3H), 5.08(d, J=4.5Hz, 1H), 5.78(d, J=4.5Hz, 1H), 6.50(s, 1H), 6.66(s, 1H) [CDCl ₃ —CD ₃ OD] |
| 2 | cis | H | — | H | CH=CH ₂ | H | H | 1765, 1700sh, 1650, 1615 | 3.60, 3.74(ABq, J=17Hz, 2H), 5.17(d, J=5Hz, 1H), 5.32(d, J=11Hz, 1H), 5.53(d, J=17Hz, 1H), 5.83(d, J=5Hz, 1H), 6.50(s, 1H), 6.61(s, 1H), 7.12(dd, J ₁ =11Hz, J ₂ =17Hz, 1H) [CDCl ₃ —CD ₃ SOCD ₃ —CD ₃ OD] |
| 3 | cis | H | — | H | CH ₂ OCOMe | H | H | 1779, 1717, 1615 | 2.10(s, 3H), 6.55(s, 1H), 6.87(s, 1H) [CDCl ₃ —CD ₃ OD] |
| 4 | trans | H | — | H | CH ₂ OCOMe | H | H | 1780, 1730, 1650 | 2.10(s, 3H), 5.73(d, J=5Hz, 1H), 6.17(s, 1H), 6.97(s, 1H) [CDCl ₃ —CD ₃ OD] |
| 5 | cis | H | CH ₂ CH ₂ | Na | H | Na | Na | 3300, 3200, 2900, 1755, 1650, 1600, 1550, 1410, 1360 | 2.88(m, 4H), 4.05(m, 2H), 5.65(d, J=6.0Hz, 1H), 6.28(d, J=6.0Hz, 1H), 6.75(m, 1H), 7.00(s, 1H), 7.22(m, 1H) [D ₂ O] |
| 6 | trans | H | CH ₂ CH ₂ | Na | H | Na | Na | 3300, 3200, 2900, 1755, 1650, 1600, 1550, 1410, 1360 | 2.89(m, 4H), 4.00(m, 2H), 5.56(d, J=6.0Hz, 1H), 6.20(d, J=6.0Hz, 1H), 6.75(m, 1H), 7.18(s, 1H), 7.25(m, 1H) [D ₂ O] |
| 7 | 1:1 | H | CHMe | Na | H | Na | Na | 3380, 1758, 1640, 1580 | 1.70, 1.73(2 x d, J=7Hz, 3H), 3.5-4.5(m, 3H), 5.57, 5.63(2 x d, J=5Hz, 1H), 5.16-6.32(m, 1H), 6.67-6.83(m, 1H), 6.83, 7.24(2 x d, J=11Hz, 1H), 7.01, 7.11(2 x s, 1H) [D ₂ O] |
| 8 | exo | H | CHMe | Na | H | Na | Na | 3380, 1758, 1645, 1595 | 2.31(bra, 3H), 3.7-4.3(m, 2H), 5.51(d, J=5Hz, 1H), 6.12(d, J=5Hz, 1H), 6.68-6.77(m, 1H), 6.89-7.05(m, 2H) [D ₂ O] |
| 9 | trans | H | (CH ₂) ₂ | Na | H | Na | Na | 3320, 3200, 2900, 1760, 1655, 1600, 1550, 1410, 1360 | 2.15(m, 2H), 2.64(m, 4H), 4.00(m, 2H), 5.55(d, J=6.0Hz, 1H), 6.20(d, J=6.0Hz, 1H), 6.75(m, 1H), 7.10(s, 1H), 7.24(m, 1H) [D ₂ O] |
| 10 | cis | H | (CH ₂) ₂ | Na | H | Na | Na | 3300, 3200, 2900, 1750, 1655, 1600, 1550, 1410, 1360 | 2.15(m, 2H), 2.70(m, 4H), 4.01(m, 2H), 5.32(d, J=6.0Hz, 1H), 6.26(d, J=6.0Hz, 1H), 6.75(m, 1H), 6.97(s, 1H), 7.29(m, 1H) [D ₂ O] |

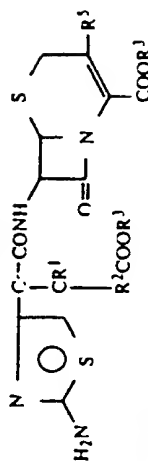


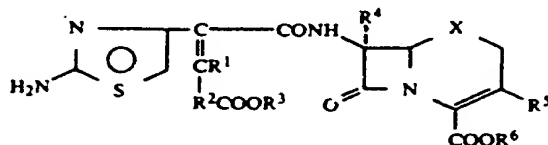
TABLE 2 (2)-continued

Carboxylic acids

| No. | cis:trans | R ¹ | R ² | R ³ | R ⁵ | R ⁶ | IR (KBr): cm ⁻¹ | NMR δ: ppm | Example No. |
|-----|-----------|----------------|---------------------------------|----------------|----------------|----------------|--|--|---------------------|
| 11 | cis | H | — | — | Na H | Na | 3400, 1760, 1690, 1570 | 1.83(s, 6H), 3.7~4.3(m, 2H), 5.63(d, J = 5Hz, 1H), 6.28(d, J = 5Hz, 1H), 6.7~6.8(m, 1H), 6.99(s, 2H) [D ₂ O] | (1-1), (3-2), (4-2) |
| 12 | trans | H | — | — | Na H | Na | 3400, 1758, 1660sh, 1600 | 1.63(s, 3H), 1.66(s, 3H), 3.74~4.30(m, 2H), 5.60(d, J = 5Hz, 1H), 6.23(d, J = 5Hz, 1H), 6.73~6.83(m, 1H), 7.08(s, 1H), 7.47(s, 1H) [D ₂ O] | (1-2), (3-2), (4-2) |
| 13 | cis | H | CD ₂ | — | Na H | Na | 3380, 3260, 1770, 1700, 1650, 1620, 1570, 1545 [Nujol] | 3.70~4.35(m, 2H), 5.65(d, J = 5Hz, 1H), 6.29(d, J = 5Hz, 1H), 6.73~6.83(m, 1H), 6.95(s, 1H), 7.06(s, 1H) [D ₂ O] | (1-2), (3-2), (4-2) |
| 14 | 1:1 | Cl | — | H H | H H | H | nd | 3.40~3.70(m, 2H), 5.13(d, J = 5Hz, 1H), 5.91(d, J = 5Hz, 1H), 6.5~6.7(m, 1H), 6.50, 6.83(2 x s, 1H) [CD ₃ OD] | (1-4), (3-2), (4-2) |
| 15 | 1:1 | Cl | (CH ₂) ₂ | H H | H H | H | 3300, 1765, 1720, 1627, 1550 | 2.8~3.15(m, 4H), 3.2~3.55(m, 2H), 3.75~4.3(m, 2H), 5.62(d, J = 4.5Hz, 1H), 6.16, 6.23(2 x d, J = 4.5Hz, 1H), 7.65~7.9(m, 1H), 7.19, 7.49(2 x s, 1H) [D ₂ O—NaHCO ₃] | (1-4), (3-2), (4-2) |
| 16 | 10:1 | Cl | (CH ₂) ₃ | H H | H H | Na | nd | 2.20~3.30(m, 6H), 3.85~4.15(m, 2H), 5.62(d, J = 3Hz, 1H), 6.23(d, J = 3Hz, 1H), 6.75(brs, 1H), 7.15, 7.55(2 x s, 1H) [D ₂ O] | (1-2), (3-2), (4-2) |
| 17 | | Cl | CH ₂ | H H | H H | H | nd | 3.8~4.3(m, 2H), 4.14(s, 2H), 5.61(d, J = 4.5Hz, 1H), 6.24(d, J = 4.5Hz, 1H), 6.74(s, 1H), 7.44(s, 1H) [D ₂ O—NaHCO ₃] | (1-4), (3-2), (4-2) |

TABLE 2 (3)

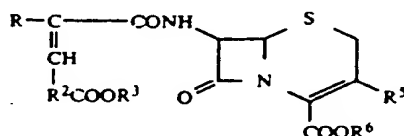
Carboxylic acids



| No | cis: trans | X | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | IR (KBr)v: cm ⁻¹ | NMR δ(D ₂ O): ppm | Exam- ple No. |
|----|---------------|---------|----------------|-----------------|----------------|----------------|--------------------|----------------|--|---|----------------------------|
| 18 | 1:2 | SO α | H | CH ₂ | Na | H | H | Na | 400, 1775, 1600, 1525, 1410, 1360. | 3.65(brd, J=8Hz, 2H), 3.85-4.15(m, 1H), 4.65-5.0 (m, 1H), 5.34, 5.43 (2 × d, J=5Hz, 1H), 6.11, 6.23 (2 × d, J=5Hz, 1H), 6.49-6.62(m, 1H), 6.99, 7.37(2 × t, J=8Hz, 1H), 7.03, 7.13(2 × s, 1H). | (1-1), (3-2), (4-2). |
| 19 | 1:1 | SO β | H | CH ₂ | Na | H | H | Na | 3400, 1770, 1600, 1525, 1410, 1360. | 3.65, 3.67(2 × d, J=8Hz, 2H), 5.42, 5.46(2 × d, J=4Hz, 1H), 6.47, 6.53(2 × d, J=4Hz, 1H), 6.55-6.62(m, 1H), 6.97, 7.52(2 × t, J=8Hz, 1H), 7.06, 7.14(2 × s, 1H). | (1-2), (3-2), (4-2). |
| 20 | 2:3 | O | H | CH ₂ | Na | OMe | CH=CH ₂ | Na | nd | 3.70(d, J=8Hz, 2H), 4.00, 4.08(2 × s, 3H), 5.0-5.3 (m, 2H), 5.55-5.90(m, 3H), 6.94, 7.40(2 × t, J=8Hz, 1H), 7.07, 7.14(2 × s, 1H), 7.0-7.50(m, 1H). | (1-2), (3-2), (4-2). |
| 21 | 1:1 | O | H | CH ₂ | H | OMe | | Na | 1773, 1670, 1630. | nd | (1-4), (3-2), (4-2). |
| 22 | 1:1 | O | H | CH ₂ | Na | OMe | | Na | nd | 3.70(d, J=8Hz, 2H), 3.99, 4.07(2 × s, 3H), 4.50(s, 3H), 5.63, 5.68(2 × s, 1H), 6.95, 7.43(2 × t, J=8Hz, 1H), 7.05, 7.13(2 × s, 1H). | (1-2), (3-2), (4-2). |

TABLE 2 (4)

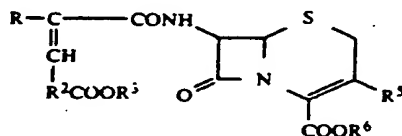
Carboxylic acids



| No | cis: trans | P | R ² | R ³ | R ⁵ | R ⁶ | IR (KBr)v: cm ⁻¹ | NMR δ: ppm | Exam- ple No. |
|----|---------------|----|-----------------|----------------|----------------|----------------|---|--|---------------------|
| 1 | trans | Ph | CH ₂ | Na | H | Na | 3400, 1760, 1650, 1585, 1510, 1410, 1365. | 3.47(d, J=8Hz, 2H), 3.65-4.25(m, 2H), 5.55 (d, J=5Hz, 1H), 6.15(d, J=5Hz, 1H), 6.66-6.76 (m, 1H), 7.30(t, J=8Hz, 1H), 7.66-8.05(m, 5H) [D ₂ O]. | (1-2), (3-2). |
| 2 | trans | | CH ₂ | Na | H | Na | 3395, 1760, 1650, 1585, 1510, 1410, 1365. | 3.70(d, J=8Hz, 2H), 3.60-4.26(m, 2H), 5.56(d, J=5Hz, 1H), 6.16(d, J=5Hz, 1H), 6.70-6.80 (m, 1H), 7.25(t, J=8Hz, 1H), 7.45-7.65(m, 2H), 7.65-8.05(m, 1H) [D ₂ O]. | (1-2), (3-2). |
| 3 | 2:8 | | CH ₂ | Na | | Na | 3400, 1760, 1660, 1590, 1385. | 3.66, 3.72(2 × d, J=8Hz, 2H), 3.90, 4.22 (ABq, J=18Hz, 2H), 4.47(s, 3H) 4.43, 4.81 (APq, J=14Hz, 2H), 5.56, 5.62(2 × d, J=5Hz, 1H), 6.08, 6.20, (2 × d, J=5Hz, 1H), 6.80, 7.26(2 × t, J=8Hz, 1H), 7.5-8.05(m, 3H). | (1-2), (3-2). |

TABLE 2 (4)-continued

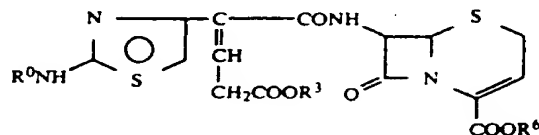
Carboxylic acids



| No | cis: trans | R | R ² | R ³ | R ⁵ | R ⁶ | IR (KBr) ν: cm ⁻¹ | NMR δ: ppm | Ex- am- ple No. |
|----|---------------|---|-----------------|----------------|----------------|----------------|---|--|----------------------------|
| 5 | 2:1 | | CH ₂ | Na | H | Na | 3420, 1760, 1655, 1585, 1413, 1365. | 3.63, 3.76(2 × d, J=8Hz, 2H), 3.73~4.33(m, 2H), 5.66(d, J=5Hz, 1H), 6.22, 6.32(2 × dd, J ₁ =5Hz, J ₂ =9Hz, 1:1), 6.7~6.83(m, 1H), 7.18, 7.43(2 × t, J=8Hz, 1H), 8.02, 8.11(2 × d, J=2Hz, 1H), 9.43, 9.51(2 × d, J=2Hz, 1H) [D ₂ O]. | (1-2), (3-2). |
| 5 | 5:4 | | CH ₂ | H | H | H | 3450, 3360, 1772, 1717, 1670, 1630, 1520. | 3.45, 3.57(2 × d, J=7.5Hz, 2H), 3.3~3.8 (m, 2H), 5.10, 5.13(2 × d, J=4.5Hz, 1H), 5.80, 5.86(2 × d, J=4.5, 1H), 6.55~6.75(m, 1H), 6.65, 6.80(2 × s, 1H), 6.67, 6.78(2 × t, J=7.5Hz, 1H) [CD ₃ OD]. | (1-4), (3-2), (4-2). |
| 6 | | | CH ₂ | Na | H | Na | 3400, 1758, 1655, 1590, 1365. | 3.76, 3.81(2 × d, J=7Hz, 2H), 4.02(m, 2H), 5.63, 5.58(2 × d, J=5Hz, 1H), 6.23, 6.32 (2 × d, J=5Hz, 1H), 6.76(m, 1H), 7.50, 7.56 (2 × t, J=7Hz, 1H) [D ₂ O]. | (1-2), (3-2), (4-2). |
| 7 | | | — | H | H | H | 3352, 1773, 1716. | nd | (1-4), (3-2), (4-2). |

TABLE 3

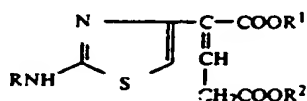
Pharmaceutical esters



| No | cis: trans | R ⁰ | R ³ | R ⁶ | (CH ₂ Cl ₃) ν: cm ⁻¹ | NMR δ(CDCl ₃): ppm | Ex- am- ple No. |
|----|---------------|----------------|----------------|----------------|--|---|----------------------------|
| 1 | cis | H | H | POM | 3420, 2980, 1780, 1750, 1660, 1630, 1530, 1480, 1390[KBr]. | 1.20(s, 9H), 3.15~3.75(m, 4H), 5.04(d, J=5Hz, 1H), 5.81, 5.92(ABq, J=6Hz, 2H), 5.90(d, J=5Hz, 1H), 6.40~6.70(m, 2H), 7.35(s, 1H). | (3-2), (4-2), (5-2). |
| 2 | 1:1 | H | H | POM | 3420, 2980, 1780, 1750, 1660, 1630, 1530, 1480 1390[KBr]. | 1.20(s, 9H), 3.15~3.75(m, 4H), 5.04, 5.06(2 × d, J=5Hz, 1H), 5.81, 5.92(ABq, J=6Hz, 2H), 5.85~5.59(m, 1H), 6.40~6.70; 6.83~7.03 (2 × m, 2H), 7.37(s, 1H) [CDCl ₃ —CD ₃ OD]. | (3-2), (4-2), (5-2). |
| 3 | 1:1 | H | POM | POM | 3395, 3320, 1790, 1753, 1685, 1110, 988. | nd | (4-3), (5-2). |
| 4 | 1:1 | H | AOM | AOM | 3380 3110, 1790, 1741, 1687, 1150, 985. | nd | (4-2), (5-5). |
| 5 | 1:1 | CBz | Bzl | POM | nd | 1.20(s, 9H), 3.00~3.90(m, 4H), 5.13(s, 2H), 5.10, 5.33; 5.15, 5.37 (2 × ABq, J=12Hz, 2H), 5.55~6.00(m, 3H), 5.85, 5.92(2 × d, J=5Hz, 1H), 6.36~6.53(m, 1H), 6.65, 7.07(2 × t, J=8Hz, 1H), 6.94, 6.96(2 × s, 1H), 7.20~7.50(m, 10H), 7.66, 8.04(2 × d, J=8Hz, 1H). | (4-2). |

TABLE 4-continued

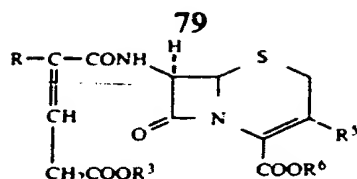
Side chain fragment acids and derivatives



| R | R¹ | R² | IR (Nujol) ν : cm^{-1} | NMR δ : ppm |
|--------------------------------|-----|------------------------------|--|---|
| 22 Cbz (1 cis: 2 trans) | H | CMe₂ CH CH₂ | 3175, 2520(br), 1732, 1659, 1071. mp. 167–168° C. (decomp.) | 1.98(s, 3H), 2.03(s, 3H), 3.82(d, J=8Hz, 4/3H), 3.86(d, J=8Hz, 2/3H), 4.87(d, J=7Hz, 2H), 5.64 (s, 2H), 5.52–5.71(m, 1H), 7.21(t, J=8Hz, 1/3H), 7.65–7.69(m, 5 + 2/3H) [CD₃SOCD₃–CD₃OD]. |
| 23 Cbz (1 cis: 2 trans) | H | CH₂ CH CMe₂ | 3150–2200, 1725, 1675, 1620, 1585. mp. 170–171° C. | 1.67(s, 3H), 1.72(s, 3H), 3.22(d, J=7Hz, 2H), 4.54(brd, J=8Hz, 2H), 5.23(s, 2H), 5.30(brt, J= 8Hz, 1H), 6.38(s, 1H), 6.99(s, 1H), 7.40(m, J=7Hz, 6H) [CD₃SOCD₃]. |
| 24 Cbz | H | CH₂ CH CHPh | nd | TLC[EtOAc/CHCl₃(1:1)]: Rf=0.2 |
| 25 H (HCl salt) | Me | Me | 3200, 1720, 1625, 1605, [CHCl₃]. | 3.44(d, J=7Hz, 2H), 3.75(s, 3H), 3.85, 3.88(2 × s, 3H), 6.70, 6.75(2 × s, 1H), 6.97, 7.43(2 × t, J=7 Hz, 1H), [CDCl₃–CD₃OD]. |
| 26 BOC (trans) | Me | Me | 3415, 1720, 1541 1155 [CHCl₃]. | 1.52(s, 9H), 3.54(d, J=6.5Hz, 2H), 3.64(s, 3H), 3.76(s, 3H), 7.11(s, 1H), 7.18(t, J=6.5Hz, 1H), 9.12(brs, 1H) [CDCl₃]. |
| 27 BOC (cis) | Me | Me | 3410, 1720, 1541, 1150 [CHCl₃]. | 1.51(s, 9H), 3.54(d, J=6.5Hz, 2H), 3.69(s, 3H), 3.83(s, 3H), 7.03(s, 1H), 7.08(t, J=6.5Hz, 1H), 9.12(brs, 1H) [CDCl₃]. |
| 28 Cbz | Me | Me | 3390, 1720, 1540 [CHCl₃]. | 3.41, 3.48(2 × d, J=8Hz, 2H), 3.65, 3.73, 3.69, 3.83(4 × s, 6H), 5.24(s, 2H), 7.00–7.37(m, 7H) [CDCl₃]. |
| 29 Clz | Et | Et | 3395, 1720 [CHCl₃]. | 1.19, 1.20, 1.22, 1.30(4 × t, J=8Hz, 6H), 3.34, 3.42(2 × d, J=8Hz, 2H), 4.08, 4.12, 4.15, 4.24 (4 × q, J=8Hz, 4H), 5.21, 5.22, 5.24(3 × s, 2H), 7.03, 7.13(2 × t, J=8Hz, 1H), 7.03(s, 1H), 7.31(s, 5H), 10.15(brs, 1H) [CDCl₃]. |
| 30 Cbz | Bzl | Bzl | 3400, 1725 [CHCl₃]. | 3.31, 3.42(2 × d, J=7Hz, 2H), 5.01, 5.03, 5.11 5.17(4 × s, 6H), 6.96–7.30(m, 17H), 10.19(brs, 1H) [CDCl₃]. |
| 31 Cbz | PMB | Bzl | nd | 3.40(d, J=7Hz, 2H), 3.75(s, 3H), 5.10(s, 2H), 5.15(s, 2H), 5.20(s, 2H), 6.8–7.4(m, 16H) [CDCl₃]. |
| 32 Cbz | BH | Bzl | 3490, 1725 [CDCl₃]. | 3.34, 3.40(2 × d, J=7Hz, 2H), 5.02, 5.05, 5.09, 5.17(4 × s, 4H), 6.8–7.4(m, 23H), 9.90(brs, 1H) [CDCl₃]. |
| 33 HCO (trans) | Me | Me | 3280, 3140, 1722, 1705, 1695 [CDCl₃] mp. 100° C. | 3.46(d, J=7.5Hz, 2H), 3.66(s, 3H), 3.78(s, 3H), 7.05(s, 1H), 7.24(t, J=7.5Hz, 1H), 8.49(s, 1H) [CDCl₃]. |
| 34 HCO (ci) | Me | Me | 3390, 3150, 1715, 1700, 1535 [CHCl₃]. | 3.56(d, J=7.0Hz, 2H), 3.73(s, 3H), 3.84(s, 3H), 7.02(t, J=7Hz, 1H), 7.12(s, 1H), 8.55(s, 1H) [CDCl₃]. |
| 35 HCO (cis) | Me | t-Bu | 3360, 1710, 1540 [CHCl₃]. mp. 101–104° C. | 1.47(s, 9H), 3.50(d, J=7Hz, 2H), 3.86(s, 3H), 7.07(t, J=7Hz, 1H), 7.13(s, 1H), 8.60(s, 1H) [CDCl₃]. |
| 36 HCO (trans) | Me | t-Bu | nd | 1.44(s, 9H), 3.27(d, J=7Hz, 2H), 3.80(s, 3H), 7.05(s, 1H), 7.31(t, J=7Hz, 1H), 8.52(s, 1H) [CDCl₃]. |
| 37 CICH₂CO (trans) | Me | Me | nd | 3.50(d, J=6.5Hz, 2H), 3.68(s, 3H), 3.79(s, 3H), 4.25(s, 2H), 7.24(s, 1H), 7.24(t, J=6.5Hz, 1H) [CDCl₃]. |
| 38 ClCH₂CO (cis) | Me | Me | 3470, 1725, 1715, 1680, 1535 [CHCl₃]. | 3.60(d, J=7Hz, 2H), 3.75(s, 3H), 3.87(s, 3H), 4.27(s, 2H), 7.18(s, 1H), 7.18(t, J=7Hz, 1H) [CDCl₃]. |
| 39 Ph₃C (3 cis: 2 trans) | Me | Me | 3380, 1720, 1703, 1500, 1480, 1425 [CDCl₃]. | 3.43(d, J=6.5Hz, 2H), 3.26, 3.64(2 × s, 3H), 3.70, 3.75(2 × s, 3H), 6.44, 6.63(2 × s, 1H), 6.54, 6.79 (2 × s, 1H), 7.01(t, J=6.5Hz, 1H), 7.25(s, 15H) [CDCl₃]. |

What we claim is:

1. A compound of the formula



wherein

- R is 2-aminothiazol-4-yl the amino group of which is unprotected or protected with a protecting group, 10
 R³ is (1) hydrogen, (2) a pharmacologically acceptable salt forming group, (3) phthalidyl, (4) phenacyl, (5) C₂₋₇alkenyl, (6) diphenylmethyl, (7) trityl, (8) phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy or (9) a lower alkyl group, 15
 R⁵ is hydrogen, methyl, vinyl, cyanovinyl, trifluoropropenyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, thiadiazolylthiomethyl, triazolylthiomethyl, aminomethylthiadiazolylthiomethyl, aminothiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio, or halogen, and 20
 R⁶ is (1) hydrogen, (2) a pharmacologically acceptable salt forming atom or group, (3) a lower alkyl group, (4) a lower alkenyl group (5) phthalidyl, (6) phenacyl, (7) diphenylmethyl, (8) trityl or (9) phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy. 25
 2. A compound according to claim 1 wherein
 R³ is hydrogen or a pharmacologically acceptable salt forming group, 30
 R⁵ is hydrogen, methyl, vinyl, trifluoropropenyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, thiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio, or halogen, and 35
 R⁶ is hydrogen or a pharmacologically acceptable salt forming atom or group. 40
 3. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid. 45
 4. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyl-3-cephem-4-carboxylic acid.
 5. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-vinyl-3-cephem-4-carboxylic acid. 50
 6. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-

butenoylamino]-3-trifluoropropenyl-3-cephem-4-carboxylic acid.

7. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid. 5

8. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxymethyl-3-cephem-4-carboxylic acid.

9. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methylthiomethyl-3-cephem-4-carboxylic acid.

10. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid.

11. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-1,2,3-triazol-5-yl thiomethyl-3-cephem-4-carboxylic acid.

12. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-1,2,3-thiadiazol-5-yl thiomethyl-3-cephem-4-carboxylic acid or 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-1,3,4-thiadiazol-5-yl thiomethyl-3-cephem-4-carboxylic acid.

13. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxy-3-cephem-4-carboxylic acid.

14. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-chloro-3-cephem-4-carboxylic acid. 35

15. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-2-fluoroethylthio-3-cephem-4-carboxylic acid. 40

16. A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-2,2,2-trifluoroethylthio-3-cephem-4-carboxylic acid. 45

17. An antibacterial composition which comprises an antibacterially effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier therefor.

18. A method for combatting bacteria which comprises bringing an antibacterially effective amount of a compound of claim 1 into contact with the bacteria.

• • • • •

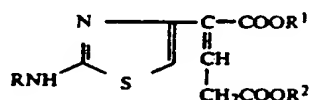
55

60

65

TABLE 4

Side chain fragment acids and derivatives



| R | R¹ | R² | IR (Nujol) ν : cm^{-1} | NMR δ : ppm |
|--------------------------------|----|--|--|--|
| 1 BOC (cis) | H | H | 3120, 1720, 1675, dp 153–154° C. | 1.50(s, 9H), 3.45(d, J=7.5Hz, 2H), 7.00(t, J=7.5 Hz, 1H), 7.13(s, 1H) [CD ₃ SOCD ₃]. |
| 2 BOC (trans) | H | H | 3150, 1700, 1630, 1600. dp 165–167° C. | 1.49(s, 9H), 3.41(d, J=7.5Hz, 2H), 6.89(t, J=7.5 Hz, 1H), 7.08(s, 1H), [CD ₃ SOCD ₃]. |
| 3 CBz | H | H | 3200, 1738, 1715, 1690. dp 169–172° C. | 3.44, 3.50, (2 × d, J=8Hz, 2H), 5.25(s, 2H), 7.07, 7.35(2 × t, J=8Hz, 1H), 7.12(s, 1H), 7.38(brs, 5H) [CDCl ₃ + CD ₃ OD]. |
| 4 HCO | H | H | 3400, 1718, 1690, 1630, 1550. dp 168° C. | 3.45, 3.63(2 × d, J=7.5Hz, 2H), 7.14, 7.32(2 × t, J= 7.5Hz, 1H), 7.23, 7.25(2 × s, 1H), 8.51(s, 1H) [CDCl ₃ + CD ₃ OD]. |
| 5 ClCH ₂ CO | H | H | 3100, 1720, 1685, 1620. dp 153–155° C. | 3.45(d, J=8Hz, 2H), 4.37(s, 2H), 6.97, 7.05(2 × t, J=8Hz, 1H), 7.23, 7.27(2 × s, 1H) [CD ₃ SOCD ₃]. |
| 6 BOC | H | Bzl | 3160, 1740, 1724, 1700, 1678, 1255, 1168. | 3.95(d, J=7.5Hz, 2H), 5.50(s, 2H), 7.26(t, J=7.5 Hz, 1H), 7.30(brs, 1H), 7.49(s, 1H), 7.75(s, 5H), 11.86(brs, 1H) [CD ₃ SOCD ₃]. |
| 7 HCO (1 cis; 2 trans) | H | t-Bu | 3150, 3100, 1720, 1690, 1635. mp 185–188° C. | 1.40(s, 9H), 3.43(d, J=7Hz, 2H), 6.89, 7.00(2 × t, J=7Hz, 1H), 7.20, 7.26(2 × s, 1H), 8.48(s, 1H). [CD ₃ SOCD ₃]. |
| 8 HCO | H | Bzl | 1735, 1690, 1620. dp 153–155° C. | 3.69(d, J=7Hz, 2H), 5.12(s, 2H), 7.17(t, J=7Hz, 1H), 7.21(s, 1H), 7.32(s, 5H), 8.46(s, 1H) [CD ₃ SOCD ₃]. |
| 9 ClCH ₂ CO | H | Me | nd | 3.39(d, J=7.5Hz, 2H), 3.70(s, 3H), 4.24(s, 2H), 7.11(s, 1H), 7.23(t, J=7.5Hz, 1H), 9.37(brs, 2H) [CDCl ₃]. |
| 10 ClCH ₂ CO | H | Bzl | 1726, 1685, 1160, dp 155° C. | 3.95, 4.01(2 × d, J=7.5Hz, 2H), 4.71(s, 2H), 5.45, 5.47(2 × s, 2H), 7.28, 7.40(2 × t, J=7.5Hz, 1H), 7.58, 7.65(2 × s, 1H), 7.70(s, 5H), 12.9 (brs, 1H) [CD ₃ SOCD ₃]. |
| 11 Cbz | H | Me | 3400–2300, 1740, 1550. | 3.58–3.73(m, 2H), 3.63(s, 3H), 5.27(s, 2H), 7.03– 7.46(m, 7H), [CD ₃ SOCD ₃]. |
| 12 Cbz (trans) | H | t-Bu | 3160–2200, 1720, 1680, 1635. mp 169–171° C. | 1.42(s, 9H), 3.53(d, J=7Hz, 2H), 5.29(s, 1H), 7.27(t, J=7Hz, 1H), 7.35(s, 1H), 7.30–7.50(m, 5H) [CD ₃ SOCD ₃]. |
| 13 Cbz (cis) | H | t-Bu | nd | 1.44(s, 9H), 3.53(d, J=7Hz, 2H), 5.27(s, 2H), 7.13(t, J=7Hz, 1H), 7.24(s, 1H), 7.30–7.47(m, 5H) [CDCl ₃]. |
| 14 Cbz (2 cis; 1 trans) | H | Me-Bzl | 3150–2050, 1720, 1670, 1620, 1570. mp. 160–163° C. | 2.33(s, 3H), 2.53, 2.70(2 × d, J=8Hz, 2H), 5.11(s, 2H), 5.26(s, 2H), 6.99–7.40(m, 10H) [CDCl ₃ –CD ₃ OD]. |
| 15 Cbz (2 cis; 3 trans) | H | Bzl | 1725, 1675, 1620, 1575. mp. 164–166° C. | 5.51, 3.73(2 × d, J=7Hz, 2H), 5.13(s, 2H), 5.26 (s, 2H), 7.06, 7.10(2 × s, 1H), 7.0–7.5(m, 11H) [CDCl ₃ –CD ₃ OD]. |
| 16 Cbz | H | Pr ⁿ B | 1720, 1575, 1515, mp. 145–148° C. | 3.80(d, J=8Hz, 2H), 3.90(s, 3H), 5.20(s, 2H), 5.33(s, 2H), 7.00(s, 1H), 6.85–7.60(m, 10H) [CDCl ₃ –CD ₃ OD]. |
| 17 H (HCl salt) | Me | H | 3330–2450, 1720, 1680, 1630. | 3.39(d, J=7Hz, 2H), 3.73(s, 3H), 6.88(s, 1H), 7.25(t, J=7Hz, 1H) [CD ₃ SOCD ₃]. |
| 18 Cbz (1 cis; 2 trans) | H | CH ₂ CH CH ₂ | 3515, 2480(br), 1736, 1549, 1305, 1086 (CHCl ₃). mp. 122–132° C. | 3.35(d, J=8Hz, 4/3H), 3.68(d, J=8Hz, 2/3H), 4.56 (d, J=6Hz, 2H), 5.11–5.37(m, 4H), 5.65–6.15(m, 1H), 6.90–7.41(m, 7H), 9.82(brs, 2H), [CDCl ₃]. |
| 19 Cbz (1 cis; 5 trans) | H | CHMe CH CH ₂ | 3420, 2500(br), 1732, 1549, 1302, 1087 (CHCl ₃). mp. 127–131° C. | 1.16(d, J=7Hz, 1/2H), 1.29(d, J=7Hz, 5/2H), 3.46 (d, J=8Hz, 5/3H), 3.68(d, J=8Hz, 1/3H), 5.05–5.49 (m, 3H), 5.16(s, 2H), 5.66–6.02(m, 1H), 7.08–7.75 (m, 7H) [CDCl ₃ –CD ₃ OD]. |
| 20 Cbz (9 cis; 11 trans) | H | CH ₂ CMe CH ₂ | 3420, 1736, 1548, 1507, 1085 (CHCl ₃). mp. 120–123° C. | 1.73(s, 3H), 3.52(d, J=8.5Hz, 11/10H), 3.73 (d, J=8.5Hz, 9/10H), 4.54(s, 2H), 4.95(brs, 2H), 5.26(s, 2H), 6.99–7.46(m, 7H), [CDCl ₃ –CD ₃ OD]. |
| 21 Cbz (1 cis; 4 trans) | H | CH ₂ CH CHMe | 3415, 1732, 1548, 1304, 1076 (CHCl ₃). mp. 139–142° C. (decomp.). | 1.67(d, J=6Hz, 3H), 3.44(d, J=8Hz, 8/5H), 3.64 (d, J=8Hz, 2/5H), 4.49(d, J=6Hz, 2H), 5.23(s, 2H), 5.35–6.05(m, 2H), 7.05–7.41(m, 7H) [CDCl ₃ –CDCl ₃]. |

EXHIBIT IV

Schering

August 25, 1988

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Food and Drug Administration
CDER - II, HFD-520
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

INVESTIGATIONAL NEW DRUG APPLICATION FOR CEFTIBUTEN
(Sch 39720), SUSPENSION - SERIAL NUMBER: 000

Dear Doctor Gavrilovich:

SUBJECT: Ceftibuten (Sch 39720), Oral-Suspension

We are herewith submitting, in triplicate, an "Investigational New Drug Application" for ceftibuten (Sch 39720), oral-suspension, as requested by the Division on August 3, 1988 in a phone conversation between Ms. Evelyn Phillips and Mr. John Nazario of your Division and Ms. Eleanor Barbo of Schering Corporation. This application separates the suspension form of ceftibuten from the capsule formulation, which is contained in Schering Corporation IND 30,303.

As codified in 21 CFR §312.10(a)(3) and discussed in the conversation with Ms. Phillips, Schering Corporation is requesting a waiver for this application of §312.23(a)(1)(iii), which requires a commitment by the sponsor not to begin clinical investigation until an IND is in effect. Since the initial clinical investigation of the ceftibuten suspension was started under IND 30,303, the request for this waiver is in accord with 21 CFR §312.40(b)(2) which allows for clinical investigation to begin upon notification by FDA. In this case, the Division has allowed investigation of the ceftibuten suspension under IND 30,303 and subsequent continuation under this new IND application which is the reason for requesting this waiver. We await notification by FDA of the assigned IND number for the ceftibuten oral-suspension.

August 25, 1988

The IND application for ceftibuten oral-suspension consists of five volumes which are organized in accord with Form FDA 1571, Item 12, as codified in 21 CFR §312.23. An overall Table of Contents is located in Volume 1, and each volume also contains a Table of Contents for that specific volume.

The information contained in this application is a resubmission of amendments previously sent to IND 30,303, which are dated December 23, 1987 (Serial No. 005) and June 10, 1988 (Serial No. 015). Additionally, information related to the ceftibuten pediatric suspension which was previously part of the July 28, 1988 amendment (Serial No. 017) to IND 30,303 is included herewith. Although these data are resubmitted, cross-reference is made to IND 30,303 for ceftibuten capsules for any chemistry, manufacturing and control data and for any preclinical and clinical data which may have relevance to the IND application for ceftibuten, as a suspension.

An initial phase I tolerance, safety and pharmacokinetic study in pediatric patients has been initiated by two separate investigators under IND 30,303. The details of this study are discussed in Attachment 6 and Attachment 9 of this application. Protocols for two additional studies are also enclosed in Attachment 6 and were previously submitted to IND 30,303 (Serial No. 017). Since we plan to start the one study (No. C88-065, "A Multidose Safety, Tolerance, and Efficacy Trial of Ceftibuten (Sch 39720) in the Treatment of Group A Streptococcal Pharyngitis, Tonsillitis and Scarlet Fever in Children and Adolescents") in the fall of this year, followed by the other study (No. C87-112, "Comparison of the Efficacy and Safety of Ceftibuten (Sch 39720) with that of Penicillin V in the Treatment of Group A Streptococcal Pharyngitis, Tonsillitis and Scarlet Fever in Children and Adolescents"), we would like to know as soon as possible if you concur with the design of these studies.

We understand that this "Investigational New Drug Application" for ceftibuten (Sch 39720) oral-suspension and all information contained therein is considered to be CONFIDENTIAL and will remain so subsequent to approval of a New Drug Application for ceftibuten, unless otherwise made public by Schering Corporation.

Sincerely,

Eleanor J. Baub for

Alexander R. Giaquinto, Ph.D.
Vice President
Regulatory Affairs

EFB/dv
Enclosures

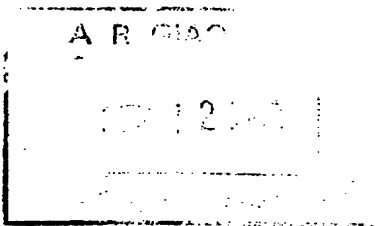


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

EXHIBIT V

Food and Drug Administration
Rockville MD 20857



SEP -6 1988

IND 32,024

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 32,024

Sponsor: Schering Corporation

Name of Drug: Cefitibuten (Sch 39720), Oral-Suspension

Date of Submission: August 25, 1988

Date of Receipt: August 29, 1988

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

IND 32,024

Page 2

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call: Mrs. Evelyne Phillips

Consumer Safety Officer
(301) 443- 6797

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drugs and Biologics, HFN-815
Attention: DOCUMENT CONTROL ROOM (12B-30)
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,



Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drugs and Biologics

CC:

Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228e (5/84)



EXHIBIT VIa

Schering-Plough
Research

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SP KEN

December 20 , 1991

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug
Products
CDER-II, HFD-520
ATTN: Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: CEDAX® (brand of cefitibuten)
Powder for Oral Suspension
New Drug Application No. 50-686

Dear Dr. Lumpkin:

Submitted herewith is our New Drug Application for CEDAX (ceftibuten) Powder for Oral Suspension, 90 mg/5 ml and 180 mg/5 ml, licensed from Shionogi & Co., Ltd. of Osaka, Japan. It is a prescription medicine, (class - cephalosporin) which is intended for once daily administration in the treatment of Pharyngitis, Otitis Media and Urinary Tract Infections.

Reference is made to a companion New Drug Application for CEDAX (ceftibuten) Capsules (NDA No. 50-865) which is being submitted concurrently with this Application. The Capsule product is intended for once daily administration in the treatment of Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis and in Urinary Tract Infections. Reference is also made to IND 32,024 under which investigations of the Powder for Oral Suspension formulation were conducted and to IND 30,303 under which investigations of the Capsule formulation were conducted.

The active ingredient is cefitibuten, a cephalosporin carboxylic acid. The drug substance, cefitibuten dihydrate, is manufactured by Shionogi & Co., Ltd. for use by Schering Corporation of New Jersey to manufacture, package and label the drug product.

Reference is made to meetings of September 14, 1988, August 31, 1990, October 9, 1990, March 25, 1991 and April 25, 1991 where design of the clinical program and subsequently the content and format of this NDA were defined. Please refer to our Minutes of Understandings from these meetings which were submitted November 15, 1988 (IND 30,303 serial number: 023), February 26, 1991 (IND 30,303 serial number: 050), and May 10, 1991 (IND 30,303 serial number: 060).

At the End of Phase II meeting on September 14, 1988, Phase II clinical study results for lower respiratory tract infections were presented and plans for the Phase III clinical program in lower respiratory tract infections, urinary tract infections, pharyngitis and otitis media were discussed. The plans for comparators, projected numbers of evaluable patients, single blind study designs, and conduct of multicenter studies both in the U.S. and internationally were all acceptable to the Division.

At the August 31, 1990 Clinical Pre-NDA meeting, the planned indications, dosage regimens and clinical study results for the Capsule and Suspension NDAs were reviewed. The NDA clinical pharmacology program was also reviewed including food interaction studies. The Biopharmaceutics Division requested three additional studies: ranitidine interaction, multiple dose pharmacokinetics of cefitibuten 400 mg once daily in adults and an antacid interaction study. Requested studies which were not completed by NDA submission could be submitted during the review period. NDA format plans for general organization, integrated safety and efficacy summaries, presentation of adverse events, Case Report Forms to be included, and safety summaries of Japanese clinical investigations were all acceptable.

At the follow-up October 9, 1990 Clinical Pre-NDA meeting with Drs. Lumpkin and Burlington, agreements were made on the nature and extent of clinical data to be included in each NDA in support of the proposed indications. The background for these agreements as well as the agreements themselves are reviewed in the Application Summary - Overview of Clinical Investigations in Volume 1.2, Section H.II.B, pages 02 0152 to 02 0162.

At the March 25, 1991 Clinical Data Listing meeting with Drs. Leissa and Albuerne, final clinical data listing formats incorporating Dr. Leissa's requests were reviewed and agreed upon. "Patient Profiles" would be prepared for each patient and included in the NDA as Case Report Tabular Summaries. Listings of "Summary Patient Information" would be included in each clinical study report as an Appendix.

At the April 25, 1991 Chemistry Pre-NDA meeting with Mr. Silver, our plans for manufacture of the drug substance involving sourcing of intermediates, lot combination for drying and surface area specifications were reviewed. The impurity/decomposition profile was also reviewed along with shelf-life and storage conditions. Finally, our plans for manufacture of the drug product including stability overcharge and nitrogen overlay for the suspension product were discussed. Our plans were acceptable.

Our non-clinical toxicology program was submitted for review and agreement on November 9, 1989 (IND 32,024 serial number: 016). In a teleconference with Dr. Browder on December 15, 1989, it was agreed that the only additional studies needed for the Suspension NDA were one month multidose studies in 4 day old rats and in 2 week old dogs in order to support pediatric use down to 6 months of age.

Our toxicology program consisting of both completed and planned studies to support the safety of degradation (related) compounds in cefibuten product were submitted for Agency agreement on June 8, 1990 (IND 32,024, serial number:026). During a July 27, 1990 teleconference and subsequently at the Chemistry Pre-NDA meeting of April 25, 1991, the Agency appeared satisfied with our toxicology programs and chemical characterization.

With regard to the environmental assessment (EA) requirement, a telephone call was held with Dr. Sheldon on September 20, 1991 to discuss Schering's proposal for submission of required information in this NDA. As per this conversation, we are providing an interim EA which includes all available information and we note in each section, as appropriate, the additional information required and target dates for that information to be provided.

This application consists of 122 Volumes which are submitted according to 21 CFR 314.50. The application is organized into Sections 1 -13 following the format of Application Form FDA 356h which accompanies this Application. The Location Index, which is included in Volume 1.1 itemizes the overall contents of the entire NDA. In addition, each individual Volume contains a detailed Table of Contents for that Volume. Each Section is numbered sequentially from 1 through to the end of the Section except for the Clinical Data Section which is numbered sequentially within each subsection. The case report forms have been submitted only with the Archival copy.

A Desk Copy of the Case Report Tabular Summaries containing individual Patient Profiles is being provided under separate cover to Dr. Leissa, the Medical Reviewer, at his request.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C, Section 331 (j).

Sincerely,



Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs

DBG:kw



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 50-686

EXHIBIT VIB

D. B. GIVEN

JAN 9 1992

Food and Drug Administration
Rockville MD 20857

Douglas B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

JAN 7 1992

Dear Dr. Given:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cedax (ceftibuten) Powder For Oral Suspension

Date of Application: December 20, 1991

Date of Receipt: December 23, 1991

Our Reference Number: NDA 50-686

Unless we find the application not acceptable for filing, the filing date will be February 23, 1992.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact Mr. Carmen DeBellas, Project Manager at 301-443-6797.

Sincerely yours,

James D. Bona, R.Ph.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 50-685
NDA 50-686

EXHIBIT VII

Food and Drug Administration
Rockville MD 20857

Schering-Plough Corporation
Attention: Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs
Gallop Hill Road
Kenilworth, New Jersey 07033

DEC 20 1995

Dear Dr. Giaquinto:

Reference is made to your new drug applications (NDA's) dated December 20, 1991 submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Cedax Capsules (ceftibuten capsules), NDA 50-685 and Cedax Oral Suspension (cefibuten for oral suspension), NDA 50-686.

We acknowledge receipt of your amendment dated November 20, 1995 submitted to each application.

Please also refer to the Food and Drug Administration's (FDA) nonapprovable letter for NDA 50-685 dated March 22, 1993 and the approvable letters for both NDA's 50-685 and 50-686 dated December 29, 1994 and September 7, 1995.

We have completed the review of these applications as amended, and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the draft final printed labeling dated December 20, 1995. Accordingly, the applications are approved effective on the date of this letter.

Marketing these products with labeling that is not identical to the enclosed labeling dated December 20, 1995, may render these products unapproved new drug products.

Please submit fifteen copies of final printed labeling (FPL), identical to the enclosed labeling dated December 20, 1995. Seven copies of the final printed label should be individually mounted on heavy-weight paper or similar material. These submissions should be designated for administrative purposes as "FPL for approved NDA's 50-685 and 50-686." Approval of these submissions by the FDA is not required before the labeling may be used.

Should additional information relating to the safety and effectiveness of these drug products become available, further revision of the labeling may be required.

NDA 50-685

NDA 50-686

Page 2

Please note that any advertising or promotional labeling for Cedax[®] Capsules and Cedax[®] Oral Suspension will be considered false and misleading under Section 502 of the Act if it utilizes in vitro microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. In vitro microbiologic data establish in vitro microbiologic activity. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties of and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for Cedax[®] Capsules and Cedax[®] Oral Suspension will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the Microbiology subsection of the drug products labeling.

Finally, any advertisement or promotional labeling for Cedax[®] Capsules and Cedax[®] Oral Suspension will be considered false and misleading under the Act if it does not include the entire INDICATIONS AND USAGE AND DOSAGE AND ADMINISTRATION sections of the labeling when referring to the indications or dosing regimens for which this product is approved. The "NOTES" and other added statements in these sections are considered integral parts of the approved indication and dosing regimens and may not be deleted or edited. Also, in advertising or promotional labeling, the "NOTES" and other added statements may not be spatially separated from the wording in the initial part of the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

NDA 50-685

NDA 50-686

Page 3

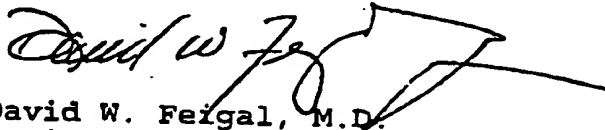
We request that you submit, in triplicate, the advertising and promotional materials you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy of the materials to the Division of Anti-Infective Drug Products and two copies of the materials to the Division of Drug Marketing, Advertising and Communications, HFD-240, Room 17B-05, 5600 Fishers Lane, Rockville, Maryland, 20857. Please submit all proposed promotional and advertising materials in draft or mock-up form, not in final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

Please submit one market package for each of the drug products of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding these applications, please contact Mr. Carmen DeBellas of the Project Management Staff at 301-827-2125.

Sincerely yours,



David W. Feigal, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

EXHIBIT IX

PAGE: 1

PATENT NUMBER: 4634697 ISSUE DATE: 01/06/87
SERIAL NUMBER: 06/711017 FILING DATE: 03/12/85
RELATED PATENT NUMBERS: 4748170
TITLE: CARBOXYALKENAMIDOCEPHALOSPORINS
APPLICANT: HAMASHIMA, YOSHIO

REEL: 4383 FRAME: 0597 DATE RECORDED: 03/12/85 NUMBER OF PAGES: 002
ASSIGNOR: HAMASHIMA, YOSHIO

EXC DATE: 03/07/85

ASSIGNEE: SHINOBI AND CO., LTD., FUKUSHIMA-KU, OSAKA, JAPAN

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST

RETURN ADDRESS: WENDEROTH, LIND & PONACK
1750 PA. AVE., N. W., STE. 1100
WASHINGTON, DC 20006

NO MORE INFORMATION FOR THIS PATENT NUMBER

NAME SHINOBI & CO., LTD. IF ASSIGNOR SEARCH ENTER Y Y

| NAME | PAT # | NAME | PAT # |
|------|-------|------|-------|
|------|-------|------|-------|

NO ASSIGNOR RECORDS

TRANSMIT FIELD

Assignment

In consideration of the sum of One Dollar (\$1.00) and other good and valuable consideration paid to each of the undersigned

YOSHIO HAMASHIMA

Insert Name(s)
of Inventor(s)

and

the undersigned hereby sell(s) and assign(s) to

Insert Name
of Assignee

SHIONOGI & CO., LTD.

Address

of Fukushima-ku, Osaka, Japan

(hereinafter designated as the Assignee) the entire right, title and interest for the United States of America as defined in 35 USC 100, in the invention known as

Title of
Invention

CARBOXYALKENAMIDOCEPHALOSPORINS

for which an application for patent in the United States of America has been executed by the undersigned

Date of Signing
of Application

on March 7, 1965

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such interference.

The undersigned agree(s) to execute all papers and documents and perform any act which may be necessary in connection with claims or provisions of the International Convention for Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States patent to the Assignee.

The undersigned hereby authorize(s) and request(s) the Commissioner of Patents to issue any and all Letters Patents of the United States resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

REEL 4383 FRAME 597

The undersigned hereby grant(s) the firm of WENDEROTH, LIND & PONACK (Registration No. 16442), Suite 1100, 1750 Pennsylvania Ave., N.W., Washington, D.C. 20006, the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent Office for recordation of this document.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s):

Date March 7, 1985, Name of Inventor Yoshio Hamashima (Yoshio Hamashima)

Date _____, Name of Inventor _____

Date _____, Name of Inventor _____

Date _____, Name of Inventor _____

Date _____, Name of Inventor _____

(This assignment should preferably be acknowledged before a United States Consul. If not, then the execution by the Inventor(s) should be witnessed by at least two witnesses who sign here.)

Witness Yuichi Ushioda Yuichi Ushioda

Witness Takayuki Wada Takayuki Wada

ACKNOWLEDGMENT

AGENCY COMMISSIONER OF
PATENTS & TRADEMARKS

MAR 12 1985

RECORDED
PATENT & TRADEMARK OFFICE

This _____ day of _____, 19____, before me
personally came the above-named _____

to me personally known as the individual(s) who executed the foregoing assignment, who did acknowledge to me that he (they) executed the same of his (their) own free will for the purposes therein set forth.

SEAL

Official Signature

Official Title

The above assigned invention may be more particularly identified as follows:

U. S. Application Serial No. _____, Filing Date _____

Title of Invention _____

REC 4 303 1005 98

94-11-01 15:00

FROM ｼｵﾉｷ ｾｲﾔｸKK K. ｼｵﾉ3F

TO 001/1-212-355-5847

PO02/003

EXHIBIT XA

WENDEROTH, LIND & PONACK
SOUTHERN BUILDING SUITE 700
805 FIFTEENTH STREET N.W.
WASHINGTON, DC 20005

DATE MAILED
07/17/90

107740

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

| ITM NBR- | PATENT NUMBER | FEE CODE | FEE AMOUNT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY YR | SML ENT | STAT |
|-------------|------------------|-------------|---------------|---------------|------------------|----------------|--------------|-----------|------------|------|
| 1 | 4,370,577 | 171 | 495 | ---- | 06/284,564 | 01/25/83 | 07/17/81 | 08 | NO | PAID |
| 2 | 4,370,673 | 171 | 495 | ---- | 06/218,012 | 01/25/83 | 12/18/80 | 08 | NO | PAID |
| 3 | 4,633,750 | 173 | 490 | ---- | 06/735,205 | 01/06/87 | 05/17/85 | 04 | NO | PAID |
| 4 | 4,634,463 | 273 | 245 | ---- | 06/650,674 | 01/06/87 | 09/13/84 | 04 | YES | PAID |
| 5 | 4,634,697 | 173 | 490 | ---- | 06/711,017 | 01/06/87 | 03/12/85 | 04 | NO | PAID |

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

| ITM NBR | ATTY DKT NUMBER |
|------------|--------------------|
| 1 | MATELOCMU737 |
| 2 | MATMU703/P41 |
| 3 | 213-K0/USP35 |

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO 20-P2229
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M, FEE, WASHINGTON, DC 20231/F4880-TW



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000513

EXHIBIT XB

75N4/0506

WENDEROTH, LIND & PONACK
ATTN: MICHAEL STONE, ESQ.
SOUTHERN BUILDING, SUITE 700
805 FIFTEENTH STREET, N. W.
WASHINGTON, DC 20005

DATE MAILED
05/06/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

| ITM NBR | PATENT NUMBER | FEE CDE | FEE AMOUNT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY YR | SML ENT | STAT |
|------------|------------------|------------|---------------|---------------|------------------|----------------|--------------|-----------|------------|------|
| 1 | 4,634,697 | 184 | 1870 | ---- | 06/711,017 | 01/06/87 | 03/12/85 | 03 | NO | PAID |

Exhibit XI
Chronology of Regulatory Activities for
CEDAX® (Ceftibuten for Oral Suspension) IND 32024

| Document Date | Document Type or Activity | Subject |
|---------------|---------------------------|---|
| 08/25/88 | IND Application | Original IND Submission for Sch 39720 Powder for Oral Suspension |
| 09/06/88 | Letter from FDA | IND has been received and number 32,024 has been assigned. |
| 09/14/88 | Meeting with FDA | Review of Clinical Plans for NDA |
| 09/30/88 | Internal memo | Summary of an end of phase II meeting held at FDA on Sept 14, 1988 to review the clinical plans for the NDA. |
| 09/30/88 | Internal memo | Difference in Schering and Shionogi suspension formulations. |
| 10/31/88 | Letter to FDA | Protocol Amendment: New Protocol for pediatric treatment of Pharyngitis, and tonsillitis and for CV's of new investigations |
| 11/30/88 | Letter to FDA | Protocol Amendment: New Protocols |
| 01/16/89 | Memo | Summary of call on 1/5/89 by FDA Doctor (medical reviewer) inquiring about pharmacokinetics data in children. |
| 01/18/89 | Letter to FDA | Protocol Amendment and New Investigator |
| 01/31/89 | Letter to FDA | Protocol Amendment: CVS of 8 New Investigators |
| 02/15/89 | Letter to FDA | Protocol Amendment and CV's of 2 new investigator |
| 02/24/89 | Memo | Summary of call from FDA: Clinical hold on study C88-070. FDA to call us on 2/27/89 re. hold |
| 02/27/89 | Memo | Summary of call from FDA which indicated reasons for the clinical hold on study C88-070. We shall receive a letter of the reasons for the clinical hold within 30 days of when we were first notified (2/24/89). Attached the memo of the 2/24/89 conversation. |
| 03/17/89 | Letter to FDA | Information Amendment Chem/Micro Submitted updated manufacturing and control information. |
| 03/24/89 | Fax from FDA | Clinical hold on C88-070 |

| | | |
|----------|-----------------|--|
| 03/27/89 | Memo | Summary of comments from FDA (fax dated 3/24/89) regarding the clinical hold on C88-070. |
| 05/01/89 | Letter to FDA | Revised the protocol for study C88-070 on clinical hold, enclosed for FDA review so we can resume the clinical trial. |
| 05/18/89 | Internal memo | The UTI protocol is under review. A conference call is being set up. |
| 05/26/89 | Letter to FDA | Protocol Amendment: CV of New Investigator |
| 06/14/89 | Memo | Discussion regarding C88-070. Summary of several phone conversations with FDA during weeks of 6/5 and 6/12/89: in a 6/9/89 call, Dr. McGill of FDA indicated she still had some concerns and needs to obtain input from Dr. Aluerne regarding UTI protocol (C88-070); and; in a 6/13/89 call, Mr. Nazario stated he was actively trying to follow up. |
| 06/20/89 | Memo | Summary of 6/20/89 phone conversation with Mr. Mazario of FDA regarding study C88-070 which is still on hold for the following major reasons: no PK data to support safety in population; have not identified rationale in out-patient population; need clearer definition for patient inclusion and exclusion criteria. FDA will fax letter to us tomorrow. |
| 06/27/89 | Letter from FDA | The revised protocol for study No C88-070 submitted on 5/1/89 (Serial No. 007) did not adequately address FDA concerns as noted in this 06/27/89 letter. This UTI study is still on clinical hold until all concerns are addressed. |
| 07/24/89 | Letter to FDA | Response to clinical hold for protocol C88-070, from FDA 6/27/89 letter. Also attached reference used to diagnose complicated UTI. |
| 07/25/89 | Internal memo | Summary of 7/19/95 phone call from FDA to advise that Brad Leissa, M.D. is the new medical reviewer for Ceftibuten. |

| | | |
|----------|-------------------|--|
| 08/03/89 | Letter to FDA | Protocol Amendment: change in Protocol; changed Protocol C87-099. Submitted final report for study C87-099. Provided revised analytical specifications and updated stability. Drug Product Attachments: Composition, Drug Product Specifications, Stability. |
| 08/28/89 | Letter from FDA | Comments on Study C87-069 |
| 09/07/89 | Letter from FDA | Fax received from FDA regarding the clinical hold on study No. C88-070. |
| 09/08/89 | Letter to FDA | Protocol Amendment: New Protocol Drug Product Attachments: Components, Composition, Packaging Components, Drug Product Specifications, Site of Manufacture, Drug Product Analytical proceed, Method of Manufacture. |
| 09/29/89 | IND Annual Report | Annual Report submitted for period: 05/31/88 to 5/31/89 |
| 10/11/89 | Internal Memo | Summary of 9/13/89 call to FDA: Schering would like to withdraw Protocol C88-070, which had been on clinical hold per FDA. FDA stated we would still receive a formal letter. |
| 10/11/89 | Letter to FDA | Protocol Amendment: CGH in Protocol Revised Protocol C87-112 to lower patient age limit for all investigators. |
| 10/11/89 | Letter to FDA | Information Amendment: Clinical Dr. Goldfard took over Dr. Blumer's studies |
| 10/11/89 | Letter to FDA | Protocol Amendment: and CV's for 2 New Investigators |
| 10/12/89 | Internal memo | Summary of calls received on 10/5/89 from FDA regarding amended C87-099 for the 18 mg/kg dose. Schering was requested not to continue with that dose in humans since the toxicology data may not support it. Because of results (the 18 mpk) in the multiple dose, Schering has no plans to continue with that dose. |
| 10/27/89 | Letter to FDA | Protocol Amendment: New Protocol Drug Product Attachments: Site of Manufacture |

| | | |
|----------|-----------------|---|
| 11/03/89 | Letter to FDA | Protocol Amendment: New Protocol The major revisions are in response to recommendations in 3/24/89 FDA fax and in relation to dose adjustment in the Otitis Media study (C88-082). |
| 11/09/89 | Letter to FDA | Information Amendment: Pharm/Tox Enclosed summary of pre-clinical toxicology and drug metabolism data for Dr. Browder's review. |
| 12/01/89 | Letter from FDA | Protocol C89-371 is on clinical hold because of inadequate toxicology data have been submitted to assess safety of single 13.5 mg/kg dose in children. |
| 12/06/89 | Letter to FDA | Protocol Amendments in pediatric groups C89-150/treatment of acute sinusitis |
| 12/07/89 | Letter to FDA | Enclosed 6 additional copies of our 11/09/89 submission as requested. |
| 12/13/89 | Letter to FDA | Submitted clinical safety data regarding study C89-241, as requested. |
| 01/05/90 | Letter to FDA | Protocol Amendment: CV's of 7 New Investigators |
| 01/15/90 | Internal memo | Summary of a conference call held on 12/15/89 to discuss the pre-clinical toxicology studies for ceftibuten suspension. Dr. Leissa (FDA) also had some comments on both the ceftibuten capsule and suspension clinical protocols and general program. |
| 02/08/90 | Letter to FDA | Submitted 2 draft toxicology protocols as requested by FDA in the 12/15/90 conference call (study numbers 90002 and 90003). Cross-reference to IND 30303. |
| 02/26/90 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: New Protocol and CV's of 3 New Investigators |
| 03/05/90 | Letter to FDA | Protocol Amendment: change in Protocol sent in response to FDA Letter of 8/28/89 regarding comments on study C87-069 (revised protocol submitted). |
| 03/15/90 | Internal memo | Summary of FDA phone call on 03/13/90 from Dr. Leissa with comments/questions on study No. C89-267. |
| 03/19/90 | Memo | Summary of 03/9/90 call from FDA regarding the two pediatric toxicology protocols, submitted on 02/08/90 and FDA agreed they were adequate to support NDA. |

| | | |
|----------|-----------------|--|
| 03/19/90 | Fax from FDA | Fax received from Dr. Leissa regarding study Nos. C89-135 and C89-150. (Sinusitis Studies) and these comments are in addition to his 12/15/89 phone conversation. |
| 03/29/90 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: New Protocol and CV's of 8 new investigators |
| 04/10/90 | Internal memo | Summary of phone comments received from FDA regarding follow-up evaluation for ceftibuten. |
| 4/11/90 | Internal memo | Summary of our phone call to FDA in response to FDA call regarding study C89-267-01. |
| 04/20/90 | Internal memo | Summary of a conference call held on 04/16/90 to discuss FDA comments on the following protocols: C88-095; C89-150; C89-135; and C89-267. FDA agreed also that adequate data were collected during Phase I and II to justify no longer measuring PT and PTT values in the Phase II studies. Summary of 4/3/90 FDA call regarding Protocol C89-113 and a 3/13/90 FDA call regarding Protocol C89-267. |
| 04/30/90 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: New Protocol and CV of new investigator |
| 05/04/90 | Letter from FDA | Refer to Amendment dated 10-27-89 for protocol C88-095. Completed review of submission, study may continue; comments made to improve quality of the data. |
| 05/04/90 | Letter from FDA | Fax (05/04/90) from FDA with comments on protocol C89-266 regarding safety concerns and other suggested changes. |
| 05/09/90 | Letter to FDA | We Withdrew protocol C88-070, C89-241, C89-371 which were placed on clinical hold, however C89-241 and C89-371 were completed prior to the call from FDA. The protocol amendment for study continues at a mpk dosing. Confirmed Dr. Browder's agreement with our toxicology protocols submitted on 02/08/90 (Ser. #021) and her agreement with toxicology program. |

| | | |
|----------|-----------------|---|
| 5/16/90 | Internal memo | Summary of 5/16/90 conference call with Dr. Leissa of FDA regarding his comments and suggestions on 4/10/90 and 4/11/90 phone calls concerning Protocol for Study C89-267-01. |
| 05/23/90 | Letter from FDA | Refer to Amendment dated 12/06/89 for protocol C89-150. Completed review of clinical portion of amendment and have comments and recommendations. |
| 06/08/90 | Letter to FDA | A meeting with reviewing Pharmacologist and chemist to discuss our planned toxicology studies to support the certification product degradation was requested. Cross-reference is made to IND 30,303. |
| 06/27/90 | Letter to FDA | Protocol Amendment: New Protocol Composition of ceftibuten oral suspension, formula 2307 is attached. |
| 06/28/90 | Letter to FDA | Summary of Pre-NDA documents: Ceftibuten related compounds and toxicology programs for degraded SCH 39720 and aged suspensions. |
| 07/26/90 | Letter from FDA | Review of the C88-117 protocol finished and comments which may improve quality of data and patient safety provided. |
| 07/27/90 | Internal memo | Toxicology plans for Ceftibuten related compounds. |
| 07/27/90 | Internal memo | Summary of two 7/27/90 calls from FDA (1) to cancel planned meeting to discuss toxicology for Ceftibuten-related compounds and (2) to provide FDA chemist's comments of his proposal revised of such product impurities/degradates. |
| 08/10/90 | Internal Memo | Summary of a call from Dr. Leissa on 07/31/90 with comments on the Pre-NDA Documents submitted on 6/28/90. |
| 08/20/90 | Letter to FDA | Information Amendment: Clinical Amendments to C87-112-17; C88-082-17; C88-082-35; C88-112-06 and C88-065-02. |
| 08/22/90 | Internal memo | Summary of a 8/21/90 FDA phone request for additional information prior to Pre-NDA meeting and clarification was received on previous FDA comments. |

| | | |
|----------|-------------------|--|
| 08/23/90 | Letter to FDA | As requested in 8/22 call we submitted information for FDA review prior to FDA 8/24/90 internal meeting and our Pre-NDA meeting on 08/31/90. |
| 08/29/90 | Internal Memo | Summary of a call on 08/28/90, among Dr. Given, Dr. Treuhaft and Ms. Babro and Dr. Lumpkin (FDA) to discuss agenda/attendees for the 08/31/90 meeting at FDA. |
| 08/31/90 | Meeting with FDA | Pre-NDA discussions of clinicals |
| 09/21/90 | Internal Memo | Summary of a Pre-NDA clinical meeting held with FDA on 08/31/90 to review the clinical studies planned for the NDA. FDA's Comments were given primarily by Dr. Burlington and Dr. Lumpkin. |
| 10/9/90 | Meeting with FDA | Pre-NDA Discussion of clinicals |
| 10/26/90 | IND Annual Report | IND Annual Report for period 06/01/89 to 05/31/90 |
| 11/07/90 | Letter to FDA | Information Amendment: Protocol Amendment |
| 12/21/90 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: |
| 02/26/91 | Internal memo | Summary of 02/26/91 phone comments from Dr. Brad Leissa on safety information, patient profiles and summary line listings on our planned NDA submissions |
| 02/26/91 | Internal memo | Summary of 02/26/91 phone conference with Dr. Ralph Harkins (statistician) to clarify populations analyzed for anti-infective divisions. |
| 02/26/91 | Letter to FDA | Minutes of understanding from the 08/31/90 and 10/9/90 Pre-NDA meetings with FDA summarizing the indications to be sought in the NDA. These will be bronchitis and complicated urinary tract infections in adults (capsule NDA) and prevaginitis and otitis media in children (suspension NDA). But, during NDA review, an additional controlled otitis media study will be amended to the unapproved NDA. |

| | | |
|-----------------------|------------------|---|
| 02/28/91 | Letter to FDA | Request for Pre-NDA technical (CMC) meeting with FDA. Summary comments for drug substance and drug product (capsule and suspension) were enclosed along with proposed agenda. |
| 03/20/91 | Letter to FDA | In preparation for 03/25/91 meeting the following was submitted: agenda attendees examples of patient profiles and summary listings of patient information and proposed outlines of ISE and ISS. |
| 03/25/91 | Meeting with FDA | Pre-NDA clinicals outlines of ISC and ISS |
| 03/27/91 and 03/28/91 | Memo | Summary of 3/27/91 and 3/28/91 phone calls to Dr. Leissa who conveyed the divisions requirements for a sinusitis indication. |
| 03/28/91 | Memo | Summary of a 3/28/91 phone call from Dr. Leissa who made additional comments in data listings for NDA and the importance of follow-up clinical outcome information for a substantial proportion of the patients. |
| 03/29/91 | Letter to FDA | Letter sent to inform FDA to efficacy data will not be used from Dr. Mohini Khurama's study center (C87-112-18) in the final study report (only safety data will be used) due to randomization inconsistencies. |
| 03/29/91 | Letter to FDA | Letter sent to notify FDA that study C87-112-18 for Dr. Khurama will not be included in the efficacy results due to randomization inconsistencies found in the study records. |
| 04/01/91 | Memo | Summary of two phone calls (1) on 04/01/91: in response to a question from our Dr. Treuhaft on the acceptability of using some of the same investigators for a second otitis media study, and (2) on 04/01/91 Dr. Leissa requested clinical and microbiological information on the first completed study. While a second study will be necessary it may not need microbiology at entry if we have sufficient microbiology from the first study. |

| | | |
|----------|------------------|---|
| 04/02/91 | Internal memo | Minutes of 03/25/91 meeting at FDA with Dr. Albuerenc and Dr. Leissa to review data listings and patient profiles. |
| 04/08/91 | Letter to FDA | Information Amendment: Protocol Amendment: |
| 04/08/91 | Letter to FDA | Information Amendment: Protocol Amendment: |
| 04/10/91 | Internal memo | Summary of FDA comments regarding follow-up evaluation for Ceftibuten Protocols |
| 04/16/91 | Letter to FDA | Letter sent to FDA confirming 04/25/91 meeting for Pre-NDA Technical data. |
| 04/25/91 | Meeting with FDA | Pre-NDA technical data. |
| 4/30/91 | Internal memo | Summary of Pre-NDA Technical Meeting at FDA on 4/25/91. |
| 05/03/91 | Letter to FDA | Submitted toxicology study reports. |
| 06/06/91 | Internal memo | Summary of FDA 06/06/91 phone conversation concerning final NDA data list formats and Leissa's requests on patient profiles and comments on protocols C90-040 and C90-886. |
| 06/27/91 | Memo | Summary of phone comments received from Brad Leissa, MD medical reviewer on 6/26/91 and 6/27/91 regarding two protocols, C90-037 and C90-045, which had been submitted for review. These studies are intended to support safety comparisons with augmentin and suprax to be made in advertising. |
| 07/12/91 | Memo | Summary of 07/12/91 phone conversation wherein Dr. Kammer reviewed with Dr. Leissa (FDA) our thinking in why further monitoring of platelets in Ceftibuten studies would have little value, it was agreed that platelet counts would not be required in the protocol but that there will be a separate field for them in the case report from so that if the information is available that it can be collected. |
| 08/16/91 | Letter to FDA | Protocol Amendment: A draft of this protocol was previously submitted on 05/17/91 (Serial No. 041) and discussed with Dr. Leissa on 06/06/91. |

| | | |
|----------|---------------|--|
| 09/20/91 | Memo | Summary of a 9/29/91 phone call wherein Schering's proposal for the Ceftibuten EA and the validation plans for the NDA were discussed with Mr. Al Sheldon (supervisory chemist). |
| 10/18/91 | Memo | Summary of 10/18/91 phone call to Dr. Leissa regarding "organization of clinical study reports and additional analyses in the NDA's". |
| 10/18/91 | Letter to FDA | A final version of protocol C90-037 (otitis media without tympanocentesis) incorporating division comments was submitted. |
| 11/04/91 | Memo | Summary of 11/04/91 phone call to Mr. Silver regarding Proposal for Ceftibuten validation batches. Mr. Silver (reviewing chemist) to follow up our submission to Mr. Sheldon (supervisory chemist) Sept. 24, 1991. Silver advised proposal acceptable; suggested we contact district office, silver also suggested that for the NDA we tabulate all manufacturing, controls and packaging sites, testing activities performed. |
| 11/14/91 | Memo | Summary of 11/14/91 phone comments on protocols C90-037, C90-045, C90-038, C91-248 by Dr. Leissa. |
| 11/14/91 | Letter to FDA | Information Amendment: Protocol Amendment: and CV's of two new investigators. |
| 11/27/91 | Internal memo | Minutes: Our Response to FDA anti-infective draft policy meeting on 11/21/91. |
| 12/18/91 | Internal memo | Impact of FDA anti-infective Draft Policy Statement on Ceftibuten Program. (at Anti-Infectives Advisory Meeting on 10/30-31/91) |
| 01/08/92 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 01/17/92 | Memo | Summary of a 1/17/92 Conference call-between Dr. Kammer, Reidenberg and Treuhaft and Ms. Rubin of Schering and C. DeBellis and Dr. Leissa of FDA concerning. Protocol C90-037 - severity of diarrhea, sample size, inclusion of antibiotic failures. |
| 01/17/92 | Letter to FDA | Protocol Amendment: New Investigator |

| | | |
|----------|-------------------|--|
| 01/21/92 | Internal Memo | Summary of a 01/21/92 call from Leissa regarding Cedax suspension - Study C90-047-01 Review on to reconstitution directions. |
| 01/21/92 | IND annual report | IND Annual Report for period 06/01/90 to 05/31/91 |
| 01/29/92 | Letter to FDA | Protocol Amendment: New Investigator and CV's for 2 new investigators |
| 02/18/92 | Letter to FDA | Protocol Amendment: New Investigator and CV's for 7 new investigators |
| 03/26/92 | Letter to FDA | Protocol Amendment: Change in Protocol and Summary of understandings from phone conferences of 02/14/91 and 02/19/91 and FDA letter to Dr. Giaquinto of 3/11/91 on adequacy of clinical studies in NDA to support otitis media indication and recommendations on additional data needed. |
| 03/30/92 | Letter to FDA | Protocol Amendments for C90-037 and C90-880 |
| 03/30/92 | Letter to FDA | Protocol Amendment: Change in Protocol: Review of agreement made with division on clinical studies for otitis media indication, timing of the review of suspension NDA and timing of the review of submission of additional data for otitis. Two ongoing otitis protocols that were revised to address these agreements are submitted. |
| 04/07/92 | Letter to FDA | Protocol Amendment: New Investigator and CV's for 9 new investigators |
| 04/23/92 | Letter to FDA | Protocol Amendment: Change in protocol |
| 05/04/92 | Letter to FDA | Protocol Amendment: Change in Protocol: New Investigator and CV's for 2 new investigators |
| 05/06/92 | Letter to FDA | Protocol Amendment: and CV's of 5 New Investigators |
| 05/15/92 | Letter to FDA | Change project physician from Jackson to Reidenberg for suspension. |
| 05/16/92 | Internal Memo | Summary of call was received from Dr. Leissa regarding study C89-267 (penetration of middle ear fluid: and a conference call on 05/16/90 responding to his questions. |

| | | |
|--------------------------|----------------------|---|
| 06/05/92 | Letter to FDA | Information Amendment: Chem/Micro Protocol Amendment: New Protocol and CV of a new investigator |
| 06/23/92 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 09/03/92 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 09/09/92 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 09/10/92 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 09/28/92 | Letter to FDA | Protocol Amendment: Draft Protocol |
| 10/05/92 | Memo | Summary of a 10/5/91 phone call regarding design of sinusitis studies, plans for otitis media electronic files, status of NDA review of market support studies discussed with Dr. Leissa |
| 10/29/92 | IND Annual Report | Annual Report for period 06/01/91 to 05/31/92 |
| 12/09/92 | Letter to FDA | Information Amendment: Clinical Study C90-037-01 |
| 12/22/92 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: change in Protocol |
| 02/02/93 | Letter to FDA | Information Amendment: Clinical |
| 02/03/93 | Letter to FDA | Protocol Amendment: CV's of 17 New Investigator |
| 02/18/93 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: CA of New Investigator |
| 03/17/93 | Letter to FDA | Information Amendment: Clinical Protocol Amendment: change in Protocol |
| 03/23/93 | Letter to FDA | Protocol Amendment: New Protocol Protocol Amendment: and CV's of 18 New Investigators |
| 04/09/93 and 04/10/93 | Internal Memo | Summary of 04/09 and 04/10/93 requests by Leissa for Protocol C90-886, overall key of abbreviations, disks of revised efficacy tables. |
| 04/28/93 | Letter to FDA | Protocol Amendment: CV of New Investigator |
| 05/13/93 | Letter to FDA | Information Amendment: Clinical: 2 site closures |
| 05/21/93 | Letter to FDA | Protocol Amendment: change in Protocol Addition of project physician - Reidenberg addition of research facilities. |
| 06/11/93 | Letter to FDA | Information Amendment: Clinical: site closed |

| | | |
|----------|-------------------|---|
| 07/08/93 | Letter to FDA | Information Amendment: Clinical: 2 sites closed |
| 10/20/93 | IND Annual Report | IND Annual Report submitted for period 06/01/92 to 05/31/93 |
| 12/13/93 | Letter to FDA | Information Amendment: Clinical Study C90-886-07. |
| 01/07/94 | Internal Memo | Summary of a 01/07/94 call to FDA: The new medical reviewer officer Cedax is Dr. Janice Soreth. She will pick up the review of the capsule NDA and has started looking at the Bronchitis Amendment of 11/15/93. Plans are underway to meet with her. Dr. Leissa will finish his review of the suspension NDA before leaving the division (end of January/early February). |
| 02/10/94 | Internal Memo | Summary of a 02/10/94 call made to Carmen DeBellis to determine the status of the suspension review. |
| 02/25/94 | Internal Memo | Summary of a call made to Dr. Leissa to discuss his 2/22/94 and 2/23 and 2/24/94 E-mails. The discussion related to the criteria for how the micros and clinical EOT and EXT were determined. |
| 03/21/94 | Memo to FDA | Summary of a call with Leissa to discuss status of Ceftibuten suspension review. (Leissa from Lamendola) |
| 04/27/94 | Letter to FDA | Information Amendment: Clinical Final Study Report |
| 06/14/94 | Internal Memo | Summary of a 6/14/94 call to FDA to discuss update regarding review status for suspension and capsule review. |
| 08/24/94 | IND Annual Report | Annual Report for period 06/01/93 to 05/31/94 |
| 10/25/94 | Letter to FDA | Information Amendment: Chem/Micro Submitted revised IND specifications. Corrected typographical error. |
| 10/28/94 | Letter to FDA | Adverse Drug Reaction 10 day initial written safety report. |
| 11/29/94 | Letter to FDA | Adverse Drug Reaction 15 day alert |
| 01/16/95 | Letter to FDA | Protocol Amendment: New Protocol P94-117 entitled: "Blind, Parallel Study Comparing Cedax Oral Suspension to Augmentin Oral Suspension in the Treatment of Acute Otitis Media." |

| | | |
|----------|-------------------|--|
| 02/03/95 | Letter to FDA | Protocol Amendment: New Protocol |
| 02/16/95 | Letter to FDA | Protocol Amendment: Change in Protocol Submitted Revised Protocol (Amendment Date 1/31/95) and the Summaries of Changes. |
| 04/13/95 | Letter to FDA | Information Amendment: Chem/Micro: IND specs for Ceftibuten Placebo Powder for Oral Susp. Formula 3069 with Formulation & Manufacturing information. |
| 04/18/95 | Letter to FDA | Protocol Amendment and CV's of 10 New Investigators. |
| 05/03/95 | Letter to FDA | Information Amendment: Chem/Micro: Submitted an updated method of manufacture for Ceftibuten. Powder for Oral Suspension 18 & 36mg./ml. |
| 05/04/95 | Letter to FDA | Protocol Amendment: Change in Protocol: Submitted 2 Amendments to this Protocol Amendment 1 (4/11/95) and Amendment s1 (2/23/95). |
| 05/12/95 | Meeting with FDA | CEDAX Suspension approval. |
| 05/15/95 | Internal Memo | Minutes of 5/12/95 FDA Meeting Re: Cedax. |
| 05/18/95 | Letter to FDA | Protocol Amendment and CV's of 5 New Investigators. |
| 06/28/95 | Letter to FDA | Protocol Amendment: CV of New Investigator. |
| 08/02/95 | Letter to FDA | Protocol Amendment: New Invest. |
| 08/23/95 | Letter to FDA | Adverse Drug Reaction 10 Day Alert |
| 08/28/95 | Letter to FDA | Protocol Amendment: CV's of 18 New Investigators. |
| 09/05/95 | Letter to FDA | Adverse Drug Reaction 10 Day Alert |
| 09/05/95 | Internal Memo | Summary of a 09/05/95 call to C. DeBellas to discuss status of Cedax Suspension/Capsule review |
| 09/14/95 | Letter to FDA | Protocol Amendment: Change in Protocol |
| 09/29/95 | Letter to FDA | Protocol Amendment: Change in Protocol, and CV's of 4 New Investigators. |
| 10/03/95 | IND Annual Report | IND annual report for period 06/01/94 to 05/31/95. |
| 10/05/95 | Letter to FDA | Information Amendment: Clinical: Submitted Final Study Reports for P91-016, P92-021 |
| 11/10/95 | Letter to FDA | Protocol Amendment: Change in Protocol, and CV's for 2 New Investigators |

| | | |
|----------|---------------|--|
| 12/20/95 | Letter to FDA | Protocol Amendment: CV of New Investigator |
|----------|---------------|--|

EXHIBIT XII
CHRONOLOGY OF REGULATORY ACTIVITIES FOR
CEDAX® (CEFTIBUTEN FOR ORAL SUSPENSION)
UNDER
NDA 50-686

| Date | Document Type/Activity | Subject |
|----------|------------------------|---|
| 01/17/91 | Internal Memo | Ceftibuten NDAs - Patient profiles on electronic files. |
| 12/20/91 | Internal Memo | Ceftibuten NDAs. Agreement on 6 month safety update Dr. Leissa requested for one line listings on Lotus 1-2-3 and loan of laser printer to assist in review of NDA's. |
| 12/20/91 | NDA Submission | NDA Submission - Cedax submission and capsules |
| 12/20/91 | Letter to FDA | Desk copy of CRFS and notification of NDA delivery on 12/20/91. |
| 01/06/92 | Internal Memo | Ceftibuten NDA medical reviewers request for verification of completeness of patient profiles and for electronic files of all patient profiles of Lotus 1-2-3. |
| 01/07/92 | Letter from FDA | Acknowledgement letter from FDA for receipt Cedax NDA. |
| 01/09/92 | Internal Memo | Ceftibuten NDAs. Medical reviewer request for an additional volume of all table of contents in NDA. |
| 01/09/92 | Memo | Administrative CMC questions from FDA reviewing chemist. |
| 01/13/92 | Internal Memo | Cedax information regarding a non-valuable patient requested by Dr. Leissa. |
| 01/13/92 | Letter to FDA | Submission of Ceftibuten overall table of contents for capsules and suspension. |
| 01/14/92 | Letter to FDA | Submission of disk copy of overall T of C for Cedax caps. |
| 01/17/92 | Internal Memo | Ceftibuten NDAs - FDA request for table of contents volume. |
| 1/20/92 | Internal Memo | Summary of a 1/17/92 phone call from Mr. Silver (FDA reviewing chemist) regarding environmental assessments, manufacturing sites and controls and methods validation. |

| | | |
|----------|------------------|---|
| 1/21/92 | Internal Memo | Summary of a 1/21/92 phone call from Dr. Leissa re: Cedax suspenses formulation |
| 01/22/92 | Internal Memo | Ceftibuten NDAs - Schering will provide table of contents for appendix C-1 for all study reports. PRE-NDA meeting planned for 2/10/92. |
| 1/23/92 | Internal Memo | Summary of phone call regarding Ceftibuten NDA to Dr. Leissa. Medical reviewer and his request for location of microbiology tables, Request for additional microbiology tables, request for table of contents for each study report with NDA volume referenced for FDA review on 02/10/92 |
| 01/24/92 | Internal Memo | Summary of a phone Call to Dr. Vincent (environmental assessment office - CDER) as requested by Mr. Silver on 01/17/92, anti-infective reviewer, to determine whether her had any comments on our plans for environmental assessment studies. |
| 01/24/92 | Memo from FDA | Cedax NDA - request from Dr. E.L. Hage for information on domestic pivotal study sets only. |
| 01/27/92 | Letter to FDA | Submission of appendices T of C for suspension. |
| 01/28/92 | Memo to FDA | Ceftibuten NDAs - medical reviewers orientation to the NDA meeting and orientation to loaner PC computer. |
| 01/28/92 | Letter to FDA | Proposal for particle electronic file submission. |
| 01/29/92 | Internal Memo | Ceftibuten NDAs - discrepancies in patient numbers. Resolution faxed to FDA. |
| 02/03/92 | Letter to FDA | Notification of computer delivery to Brad Leissa - Ceftibuten medical reviewer. |
| 02/04/92 | Letter to FDA | For Ceftibuten NDA's testing of investigators for domestic pivotal studies numbers patients per site and protocols for each indication of investigation branch. |
| 02/04/92 | Meeting with FDA | Orientation CEFTIBUTEN NDA. |

| | | |
|----------|---------------|--|
| 02/04/92 | Internal Memo | Summary of phone call from Mr. Silver in follow-up to earlier conversation on 01/17/92 regarding the Ceftibuten capsule and suspension NDA's. Informed him of 01/29/92 conversation with Dr. Vincent and Dr. Graham. Japanese sites to be ready for inspection late September 1992. Scale-up batches of drug products have been manufactured in Miami Lakes at 40-100% commercial scale. |
| 02/04/92 | Letter to FDA | Orientation program outline given to Leissa and Debellas, of FDA on 02/04/92 |
| 02/06/92 | Letter to FDA | Appendices table of contents for study reports in suspension. |
| 02/07/92 | Internal Memo | Summary of phone call on Ceftibuten NDA: medical reviewer's question on rational for 200 ng requirements for safety update. |
| 02/10/92 | Internal Memo | Summary of phone call on Ceftibuten NDA: - medical reviewer questions. |
| 02/10/92 | Internal Memo | Cedax capsule/suspension 45 day meeting. |
| 02/10/92 | Letter to FDA | Replacement pages for application summary and clinical data section. |
| 02/11/92 | Internal Memo | Summary of FDA meeting minutes - orientation to NDA for medical reviewer comments on protocol C90-037. |
| 02/12/92 | Internal Memo | Summary of a phone call to Dr. Vincent: Follow up with Dr. Vincent to our telephone call of 01/29/92. He has not yet reviewed the Ceftibuten capsules and powder for oral suspension environmental assessments. He will call after he has completed his reviews. |
| 02/12/92 | Internal Memo | Summary of phone call on Ceftibuten NDA's - Medical reviewer questions on pharyngitis patient profile, div. guidance on requirements for sinusitis indication. |
| 02/13/92 | Internal Memo | Revised minutes of 02/04/92 FDA meeting (orientation to Ceftibuten NDA's) |
| 02/14/92 | Internal Memo | Filing for Cedax NDA. Summary of Teleconference of 2/14/92. |
| 02/14/92 | Memo to FDA | Ceftibuten filing of the NDA's and the otitis media indication. |
| 02/15/92 | Internal Memo | Otitis media - filing and need for additional data. |

| | | |
|----------|---------------------|--|
| 02/18/92 | Letter from FDA | E-mail connection with medical reviewer. |
| 02/21/92 | Letter from FDA | Medical reviewer request for table of contents on disks. |
| 02/21/92 | Letter from FDA | Request for status of Beta-Lactamase data from LRTI studies. |
| 02/26/92 | Memo from FDA | Medical reviewer (Dr. Leissa) requests. |
| 02/28/92 | Memo from FDA | Clinical study report revisions and confirmation of filing of the NDA's by Dr. Leissa. |
| 02/28/92 | Memo to FDA | FDA phone report regarding "partial electronic file submission". |
| 02/28/92 | Letter from FDA | Medical reviewer (Dr. Leissa) request for application summaries in Word Perfect files. |
| 02/28/92 | Memo from FDA | Request for appendiceal table of contents by Dr. Leissa. |
| 03/03/92 | Letter to FDA | Per requests of 02/21/92 and 02/28/92, Submission of appendiceal table, table of contents on disc, patient profiles of LRTI, submission of instruction of installing LRTI files letter to Mr. Moss authorizing installed of virus protection software. |
| 03/04/92 | Letter to FDA | Submission of CSR appendicial tables on disc and T of C, LRTI patient profile, instruct for installing LRTI files copy of letter to Mr. Moss. |
| 03/05/92 | Internal Memo | Content of otitis media Amendment. |
| 03/11/92 | Letter from FDA | Reference to the filing of both capsule and suspension NDA. Reference to telephone conversation in Feb regarding the filing of otitis media. |
| 03/12/92 | Fax letter from FDA | Fax sent by Mr. Debellas (CSO) with comments on Ceftibuten environmental assessment by Dr. Vincent, environmental assessment office. |
| 03/13/92 | Letter to FDA | Analytical methods validation. Submitting copy of letter sent with samples to Dr. Graham 02/12/92 together with storage instructions, explanation of resolution test solutions and revised C of A for working reference standard. |
| 03/13/92 | Internal Memo | Safety update for suspension NDA, can follow that of capsule, division recommends by 08/01/92. A second safety update should follow otitis media amendment within one month. |

| | | |
|----------|---------------|--|
| 03/13/92 | Internal Memo | Summary of 03/11/92 call from Mr. Silver who asked about dates of manufacture, batch sizes and equipment scale for Ceftibuten capsules and suspension analytical sample sent to Dr. Graham, antimicrobial drugs branch and call to Mr. Silver on 03/13/92 to give him the requested information. |
| 03/18/92 | Internal Memo | Obtained clarification of Dr. Vincent's comments (faxed by Mr. Debellas, copy attached) on our environmental assessment for Ceftibuten; separate EA's required for capsule and suspension structure and name body of EA, must include "no action" terminology and alternative. Dr. Abramson advised that the list of fate and effects studies seems satisfactory, he had no suggestions for other tests. |
| 03/18/92 | Internal Memo | Obtained clarification of Dr. Vincent's comments (faxed by Mr. Debellas, copy attached) on our environmental assessment for Ceftibuten; separate EA's required for capsule and suspension structure and name body of EA, must include "no action" terminology and alternative. Dr. Abramson advised that the list of fate and effects studies seems satisfactory, he had no suggestions for other tests. |
| 03/18/92 | Internal Memo | NDA's - status of outstanding requests and planned targets for submission discussed. |
| 03/26/92 | Memo from FDA | Medical reviewer requests need for use in Otitis media amendment. |
| 03/27/92 | Memo from FDA | Medical reviewer requests need for use in Otitis media amendment. |
| 04/01/92 | Letter to FDA | Submitted SAS files for LRTI and Pharyngitis and copies of documentation for patient profiles discs for LRTI and Pharyngitis previously submitted to medical reviewer. |
| 04/01/92 | Letter to FDA | Listing of patients excluded from safety and efficacy analysis. |

| | | |
|----------|---------------------|---|
| 04/01/92 | Letter from FDA | Request for further clarification of field definitions in LRTI patient profiles files request for field definitions for all files for UTI. |
| 04/06/92 | Memo from FDA | Request by Leissa for information on time field of the signs table. |
| 04/07/92 | Letter from FDA | Request for resolution of discrepancies in number between signs and old signs files in LRTI Paradox files. |
| 04/08/92 | Memo from FDA | Request from Leissa for explanation of numbers of patients enrolled. Request for Paradox and Lotus files for laboratory values for safety populations for capsules and suspensions NDA's. |
| 04/15/92 | Letter from FDA | Request for additional information on concurrent anti-infective therapy. |
| 04/16/92 | Letter from FDA | Leissa request for additional info on fax of 4/16/92 relative to files and fields. |
| 04/22/92 | Letter from FDA | Questions on extended follow-up bronchitis patients. |
| 04/27/92 | Letter to FDA | Per Brad Leissa's (FDA) request, supplied disc copy of application summary. |
| 04/28/92 | Letter from FDA | Request for duration of therapy information for C88-044-04-151 and C88-044-04-153. |
| 04/29/92 | Letter from FDA | Request for extended clinical response information for patient C88-044-24-106. |
| 04/30/92 | Letter from FDA | Request for information on patient with adverse event of UTI. |
| 04/30/92 | Letter from FDA | Request for explanation of non compliance for C88-044-30-102. |
| 04/30/92 | Letter from FDA | Request for adverse event information for patient C88-044-32-107. |
| 05/19/92 | Fax letter from FDA | CMC comments concerning Cedax suspension. |
| 05/19/92 | Letter from FDA | E-Mail request regarding C88-044 study. |
| 05/21/92 | Letter to FDA | Request for meeting with medical reviewer. |
| 05/29/92 | Letter to FDA | Correspondence: request for agreement on proposal for otitis media amendment. |
| 06/01/92 | Memo to FDA | Timing of responses to outstanding requests of Leissa. |
| 06/03/92 | Letter to FDA | CEDAX Pharma/Tox reports |
| 06/11/92 | Internal Memo | Summary of call to Mr. Peter Smith regarding FDA plans for inspection of Shionogi facilities in Kanegasaki. |

| | | |
|----------|-------------------|--|
| 06/15/92 | Meeting with FDA | Meeting with FDA medical reviewer to discuss NDA. |
| 06/16/92 | Letter to FDA | FDA letter acknowledging receipt of pharm/tox reports - 06/03/92. Submission considered major amendment. |
| 06/18/92 | Letter from FDA | Leissa request for added information on I88-111-02-017, 111/I88-217-05-105, 102/I88-217-01-112. Also questioned dosing. |
| 06/18/92 | Letter from FDA | Leissa request for clinical signs/symptoms in patient profiles for I88-111-04-103. |
| 06/19/92 | Internal Memo | Summary of phone call: Leissa's requests of 6/19/92 concerning middle ear fluid levels pharmacokinetic data in bronchial secret only safety update for Nov for suspension. |
| 6/22/92 | Letter to FDA | Per 06/18/92 Request from B. Leissa for more information on patients: I88-11-03-106/107/109/110; I88-217-01-102; I88-217-05-103; I88-217-05-104; I88-217-09-103/111. |
| 06/24/92 | Letter from FDA | Leissa requested additional information on I88-217-14; 010/I88-217-17-101; 104/I88-217-231-08/I88-327-01-104; I88-327-03-02 |
| 06/24/92 | Internal Memo | Summary of a telephone conversation: Dr. Lamb called to say they used the Ceftibuten pediatric data generically for an APS poster session. |
| 06/24/92 | Letter from FDA | Leissa request for more information on C88-044-04-112. |
| 06/24/92 | Letter from FDA | Leissa request for comment pages from CRFS for bronchitis patients from I88-111; I88-217 and I88-327. This will be followed by all comment pages from all NDA studies. |
| 06/25/92 | Internal Memo | Summary of a phone Request by Leissa for comment pages from CRF for all NDA patients and for numeric definitions of letter used in laboratory normal ranges. |
| 06/26/92 | Fax letter to FDA | Per Leissas request of all CRF pages. |
| 07/01/92 | Internal Memo | Summary of a Telephone conversation with Mr. Peter Dionne regarding possible sourcing of an intermediate for Ceftibuten synthesis from a contract facility. |
| 07/02/92 | Letter from FDA | Request for 100 mg formulation from pharm sci response received. |

| | | |
|----------|-------------------|--|
| 07/02/92 | Letter from FDA | Leissa request for 1) who received 100 mg in NDA 2) where is bioequivalence data for 200/400 (answered) 3) total doses 4) I88-217-01-107/108 5) formulation ect for 100/200/100 mg (answered). |
| 07/08/92 | Letter from FDA | Request by Leissa for CRF I88-327-01-106 response via phone 7/8/92. |
| 07/08/92 | Fax letter to FDA | Per Dr. Samara's request of 7/22/92 regarding Cedax formulas. |
| 07/29/92 | Letter to FDA | CRF comments pages for PED UTI study I88-116. |
| 07/31/92 | Fax letter to FDA | Per request of 7/22/92, classifications of patients discussed at your 6-15 meeting. |
| 08/03/92 | Fax letter to FDA | Per Leissa's E-mail of 7/22/92 concerning Dr. Rolek's qualifications. |
| 08/10/92 | Letter from FDA | Leissa requests for information on UTI centers C87-069, 4/7/9/10: I87-247/1/2/3: I87-326/1/9/10/13/14/18/21/22: I87-128/4/5/6: I88-116/6/7/8 also requested info on fields - clarify. |
| 08/10/92 | Memo from FDA | More information requested on fields by Leissa. |
| 08/12/92 | Letter from FDA | Request for additional information on PT I87-325-02 009; I87-223-01 10 and request for re-examination of total doses. |
| 08/12/92 | Memo to FDA | Regulatory requirements for Phase IV studies sent to Leissa. |
| 08/13/92 | Memo to FDA | Regulatory requirements for Phase IV clinical studies. |
| 08/14/92 | Letter to FDA | Responses to CMC questions and submission of draft labelling. |
| 08/17/92 | Letter from FDA | UTI-patient C87-069-03-03 comments page marked out why? |
| 08/17/92 | Letter from FDA | Clarification re UTI C87/069/02/009 comment pages says Klebsiella Oxytoca grew, patient profile says Klebsiella Pneumoniae. |
| 08/18/92 | Letter from FDA | C87-069-01-20: comment page and profile do not match; please identify correct information. |
| 08/18/92 | Letter from FDA | E-mail request of 8/18/92 C87-069-05-018 patient profile IDA severe diarrhea as an ADR. also reported this was secondary to Clostridium difficile and received flagyl. No mention in safety summary what happened. |
| 08/19/92 | Memo from FDA | Status of medical review of Ceftibuten NDA. |

| | | |
|----------|----------------------|---|
| 08/19/92 | Letter from FDA | Leissa request for Mic/Zone size Information re I87-326-03-000 |
| 08/20/92 | Letter from FDA | E-mail requesting CRFS for 24 patients from I87-24-702 and I87-24-703. |
| 08/20/92 | Letter from FDA | Patient profiles with neurogenetic complications excluded from evaluation. Please explain. |
| 08/21/92 | Letter from FDA | Leissa request to check susceptibility for I87-326-03-011. |
| 08/21/92 | Memo from FDA | Status of request by Leissa for reconciliation of UTI patient profiles. |
| 08/26/92 | Fax letter from FDA | Biopharmaceutics reviewer from FDA for Cedax capsules. |
| 08/27/92 | Letter to FDA | Resubmission of CMC response of 8/21/92 to correct typo's. |
| 09/09/92 | Letter to FDA | Memorandum of minutes of 6/15/92 meeting with FDA reviewer. |
| 09/10/92 | Letter from FDA | Letter from FDA requesting additional info on samples and methods validation. |
| 09/14/92 | Memo to FDA | Planned improvements to computer hardware and software request for Dr. Leissa's draft review on LRTI. |
| 09/16/92 | Fax Letter to FDA | Response to 9/16/92 questions. |
| 09/17/92 | Letter from FDA | Request for total doses of study drug administered for I87-247-02 (16 patients) and 03 (8 patients). |
| 09/18/92 | Fax letter to FDA | Pre request of 9/17/92 regarding total doses. |
| 10/04/92 | Memo from FDA | Request from Leissa for additional information on I88-217-07-112, 217-08-101, 271-18-104 reason for "changing" diagnosis. |
| 10/05/92 | Memo from FDA | Design of sinusitis studies, plans for otitis media electronic files, status of NDA review of market support studies requested by Leissa. |
| 10/08/92 | Fax letter to FDA | Response to Leissa E-mail of 10/04/92 concerning 3 patients (LRTI) I87-217. |
| 10/19/92 | NDA Amendment to FDA | Otitis media amendment. |
| 10/20/92 | Internal Memo | Display of fields for suspension NDA electronic files for patient profiles. |
| 10/20/92 | Fax letter to FDA | Request from 10/9/91 concerning pneumonia patients rediagnosed as bronchitis. |

| | | |
|----------|----------------------|---|
| 10/29/92 | Internal Memo | Summary of a conversation between Leissa and Kammer agreeing to lab tests during therapy at 3-5 days and 3-5 days post therapy visit to replace 1-2 day end of treatment visit. |
| 10/30/92 | Internal Memo | Summary of a phone conversation regarding phase IIIB protocols between Schering/Leissa. Leissa gave go ahead with agreed upon corrections. |
| 11/02/92 | Letter from FDA | Otitis Media amendment sent 10/19/92 acknowledgement. |
| 11/02/92 | Internal Memo | Summary of a phone discussion with B. Leissa concerning lab files error and contacting of non-regulatory staff. |
| 11/02/92 | Letter from FDA | Request for corrected electronic pharyngitis files. |
| 11/02/92 | Memo from FDA | Submission of additional patient profiles for C90-886. |
| 11/02/92 | Letter from FDA | Acknowledgement of new "due" date for suspension. |
| 11/05/92 | Memo to FDA | Update on status of pre-clinical for cap discussion of PI with Carmen. |
| 11/05/92 | Letter to FDA | Replacement pages for 10-28-92 submission sent to capsule NDA. |
| 11/16/92 | Memo to FDA | FDA review of sinusitis/protocols, NDA review. |
| 11/30/92 | Memo from FDA | Inquiry of I87-07-00 by Leissa. |
| 11/30/92 | Letter from FDA | Review of capsule NDA, medical reviewer comments on draft sinusitis protocols C92-107 and C92-125. |
| 12/03/92 | Internal Memo | Request for resolution of pediatric UTI dosing. |
| 12/04/92 | NDA Amendment to FDA | Safety update for powder to support once daily administration. |
| 12/10/92 | Memo from FDA | Additional programming for electronic files. |
| 12/11/92 | Memo to FDA | Plans for submission on electronic files of clinical data for suspension NDA. |
| 12/16/92 | Letter to FDA | Submission of draft suspension insert for cedax. |
| 01/04/93 | Internal Memo | Status of NDA review, suspension efficacy tablets updated. |
| 01/06/93 | Memo from FDA | Countries where CEDAX is approved and DATE of approval and dosing regimen |
| 01/07/93 | Fax letter to FDA | Per 01/06/93 Request by Leissa concerning difference in 400 mg formula. |
| 01/08/93 | Memo to FDA | Response to Dr. Leissa request PF 1/7/93 regarding international approvals and dosage. |

| | | |
|----------|-----------------|---|
| 01/19/93 | Letter to FDA | Submission of new efficacy tables for pharyngitis and otitis media to be updated to reflect corrections in clinical data. |
| 01/19/93 | Letter to FDA | Replacement computer for medical reviewer. |
| 01/20/93 | Letter to FDA | Notification of installation for electronic files for pharyngitis patient profiles and laboratory data. Submission of supporting documentation including log of data corrections. |
| 01/29/93 | Memo to FDA | Arrange for submission of Cedax samples and methods validation packages. |
| 02/02/93 | Letter from FDA | Acknowledgement of pharyngitis correction files submitted 01/19/93 and received 1/20/93. Date of review now 6/19/93. |
| 02/11/93 | Memo to FDA | Status of capsule review notification Leissa will review Otitis media first. |
| 02/19/93 | Memo from FDA | 2/19/93 E-mail requesting comment pages and clinical responses. |
| 02/25/93 | Letter to FDA | Submission of electronic files and hard copy for otitis media data base corrections. |
| 03/10/93 | Memo from FDA | Update of FDA review suspension |
| 03/12/93 | Letter to FDA | Submission of updated otitis media and a copy of patient profiles. |
| 03/15/93 | Letter to FDA | Submission of comment pages per Leissa's 2/19/93 report. |
| 03/18/93 | Internal Memo | Summary of phone call to Mr. Dionne to discuss 1) submission of corrected dissolution procedures based on pre-approved inspection, 2) submission of update to manufacturing process description for powder for suspension, 3) submission of alternative suppliers of 3-alcohol intermediate for Ceftibuten. |
| 03/19/93 | Letter to FDA | Provision for CMC inconsistencies in text identified during Miami inspection and 18 and 36 mg/ml dissolution rate procedure and specs. |
| 03/22/93 | Letter to FDA | Responses to FDA 483 issue to a request on 3/8/93 by investigator Stephen J. Tunks, regarding his preapproval inspection of our Cedax operations. |
| 03/24/93 | Memo to FDA | Discussion of Ceftibuten non-approval letter and request for additional otitis media data. |

| | | |
|-----------------------|-------------------|--|
| 03/26/93 | Letter to FDA | Submission of comment page number 24 for I88-115-14 to Dr. Schloss (our submission of 3/15/93 PG 895A). |
| 04/09/93 | Memo from FDA | Dr. Leissa's request concerning clarification to the data base our 2/25/93 submission. |
| 04/09/93 and 04/10/93 | Internal Memo | Summary of 04/09/93 and 04/10/93 phone calls from Leissa: his requests for protocol C90-886, overall key of abbreviations, disk of revised efficacy tables. |
| 04/09/93 | Internal Memo | Summary of a phone call from Mr. Taylor (FDA analytical labs) with questions regarding the analytical procedure for determination of group X impurities in Ceftibuten. Dr's. Chambers and Reimann called him back to respond to his questions. Dr. Chambers arranged to lend the appropriate HPLC column to the FDA labs for assay validation for the group X related substance. |
| 04/10/93 | Memo from FDA | Questions regarding Ceftibuten suspension from Dr. Leissa. |
| 04/12/93 | E-mail from FDA | E-mail identifying active ingredients for following drugs. |
| 04/12/93 | Memo from FDA | Leissa's request of 04/12/93 regarding international drugs. |
| 04/12/93 | Memo from FDA | Questions regarding Ceftibuten suspension from Dr. Leissa. |
| 04/13/93 | Letter to FDA | Submission of mouse subdirectory on "D" diskdrive. |
| 04/13/93 | Letter to FDA | Response to Leissa's 4/9/93 request for overall key to abbreviations. |
| 04/13/93 | Letter to FDA | Disk of revised efficacy table. |
| 04/13/93 | Fax letter to FDA | Response to Leissa's request of 04/12/93 regarding international drugs. |
| 04/13/93 | Memo from FDA | Inquiry on Otitis Media amendment of 10/19/92 C88-082-01. |
| 04/13/93 | Memo from FDA | Discrepancy in total patient numbers please explain, 1/20/93 amendment were patients added or deleted? |
| 04/14/93 | Letter to FDA | Resubmission of page 151 from Feb. 02/25/93 25th submission with fields that each data value can be found in. |
| 04/15/93 | Memo from FDA | List of formulations for Otitis media studies C90-037 and C90-886 submitted in 10/19/92 Amendment. |
| 04/15/93 | E-mail from FDA | E-mail requesting formulations used in clinical trials. |
| 04/16/93 | Memo from FDA | Question on patient C90-037-10,004. |

| | | |
|-----------------------|-------------------|---|
| 04/18/93 | Memo from FDA | For each indication, please provide pages to explain centers that did not enroll patients and why. |
| 04/19/93 | Memo from FDA | What formula used for C89-267-02 difference between C88-082-16 and C88-82-01, difference between I88-115-11. |
| 04/21/93 | Memo to FDA | Response to Leissa's E-mails of 4/16/93 and 4/13/93. |
| 04/22/93 | Letter to FDA | Replacement disk sent to Dr. Leissa for use (his disk was flawed). |
| 04/28/93 and 04/29/93 | Internal Memo | Summary of a 04/28/93 Dr. Leissa call regarding the definition of armstrong tables, and our response by phone on 4/29/93. |
| 04/29/93 | Letter to FDA | Replacement disk for ISS - table SUS. |
| 04/29/93 | Memo from FDA | Leissa's request for definitions for the abbreviations used for tympanogram results in C88-082/I88-115. |
| 04/30/93 | Memo from FDA | Dr. Leissa wants confirmation of his understanding of visits vs culday entries in the database. |
| 04/30/93 | Letter to FDA | Response to 2/19/93 request for clinical response changes. |
| 05/03/93 | Letter to FDA | Response to the Leissa request of 4/9/93 for protocol C90-886 and amendments. |
| 05/04/93 | Letter to FDA | Response to 4/13/93 request for patient profiles on six patients added to safety (I88-112) these were post NDA. |
| 05/04/93 | Memo from FDA | C90-037 (7) missing patient from Leissa's database. Explain why. |
| 05/04/93 | Memo from FDA | C90-037-11-008 not in database etc. is this a typo? |
| 05/04/93 | Memo from FDA | C88-082-02-025 - final clinical response is "sustained improvement" and listing had typo. |
| 05/05/93 | E-mail from FDA | "what is definition of clinical efficacy" population what is 1 degree population "clinical efficacy" of efficacy does "efficacy" population = "valid" population? |
| 05/05/93 | Letter to FDA | Per 4/26/93 request, paradox file submitted for temperature route. |
| 05/05/93 | Fax letter to FDA | Response by fax to E-mail of 4/15/93 for clinical formulations. |
| 05/06/93 | Memo from FDA | Incomplete concomitant therapy files. This was addressed in a phone call. Dr. Leissa was mistaken. |

| | | |
|----------|---------------|---|
| 05/06/93 | Memo from FDA | Questions on C90-886-02-024 and C90-886-06-019. |
| 05/07/93 | Memo from FDA | Concerning clinical response definition on C90-037 and C90-886. |
| 05/08/93 | Memo from FDA | Leissa E-mail regarding exclusion reasons. |
| 05/08/93 | Memo from FDA | Leissa E-mail regarding otorrhea and perforation for 8 patients in I88-115. |
| 05/08/93 | Memo from FDA | E-mail concerning otorrhea and perforation. |
| 05/08/93 | Memo from FDA | E-mail from B. Leissa concerning exclusion reason C88-082-110-26. |
| 05/13/93 | Letter to FDA | Submission of Electronic Files Structurio per Dr. Leissa's request. |
| 05/14/93 | Memo from FDA | E-mail from Dr. Leissa (5/14/93) concerning validity and bacteria results of 4 pts. from C88-082-16-006; 28/C88-082-3L-005; 015. |
| 05/16/93 | Memo from FDA | E-mail form Dr. Leissa (5/16/93) concerning I88-115 evaluation blinded - why document pages indicate study drug patient randomized to "tympanostomies"? |
| 05/17/93 | Internal Memo | Inquiry as to whether a re-inspection had been rescheduled in Miami. |
| 05/17/93 | Memo from FDA | E-mail from Leissa. What happened to I88-115-12-008/009? Not in database. |
| 05/19/93 | Letter to FDA | Disk containing file NMVTV1PAT.SC from R. Eckert per Dr. Leissa's request. |
| 05/20/93 | Memo from FDA | List of patients identified in I88-115 with tympanostomies. |
| 05/23/93 | Memo from FDA | E-mail from Leissa concerning "misrandomized: patients C90-037 I88-115. |
| 05/24/93 | Memo from FDA | E-mail from Leissa requesting 1) algorithm 2) explanation for C90-037-12-028. |
| 05/24/93 | Memo to FDA | Responses to E-mails of discussion of ISE/ISS. |
| 05/25/93 | Memo from FDA | E-mail from Leissa found amended CRF's. |
| 05/25/93 | Memo from FDA | E-mail from Leissa concerning revised definitions. |
| 05/25/93 | Memo from FDA | Question concerning revised definition and patient C90-037. |
| 05/28/93 | Memo from FDA | Dosing data confusion. |
| 06/01/93 | Memo from FDA | Micro responses for C90-886. |
| 06/01/93 | Memo from FDA | Locate profile for C90-886-02005. |
| 06/01/93 | Memo from FDA | What happened to patients form C90-886-02 # 6 0-10-; 5; 18-20. |

| | | |
|----------|-----------------|---|
| 06/01/93 | Memo from FDA | Caveat to planned October 1993 submission for AEBC. |
| 06/03/93 | Memo from FDA | Noncompliance issue C90-886-02-024. |
| 06/04/93 | Internal Memo | Summary of a phone call to C. DeBellas regarding Proposed date and items for Cedax meeting proposed for July. |
| 06/06/93 | Memo from FDA | Discussion regarding UTI indication and overall Ceftibuten suspension review. |
| 06/08/93 | Internal Memo | Summary of Garaud, Lamendola, Reidenberg, Rubin, Taglietti discussion of 06/04/93 phone call with FDA. |
| 06/16/93 | Memo from FDA | Clarification EOT responses for 5 additional patients in C90-037 rev def 2. |
| 06/17/93 | Memo from FDA | Current understanding was at least 80% of calculated dose taken. |
| 06/17/93 | Memo from FDA | Further dosing clarification on C90-037-10-15. |
| 06/17/93 | Internal Memo | Summary of a Telephone conversation concerning Miami inspection and letter to Mr. Koan. |
| 06/18/93 | E-mail from FDA | E-mail from Leissa requesting clarification of response to 5/14/93 E-mail on C88-082. |
| 06/21/93 | Letter to FDA | Letter to district office in Miami responding to letter to Mr. Koan. |
| 06/23/93 | Internal Memo | Summary of a phone Conversation with C. DeBellas notifying us of review clock extensive on suspension NDA for 80 days. Also bronchitis amendment does not need statistical section. |
| 06/23/93 | Memo from FDA | Leissa's request for a walk through calculations on suspension see E-mail 6/17/93 12:00 PM. |
| 06/23/93 | Memo from FDA | Response to Maico's inquiry on definitions for micro responses. |
| 06/24/93 | Memo from FDA | Brad Leissa's request for clarification on C88-082 and C88-088 for organism response. |
| 06/24/93 | Letter to FDA | Withdrawal of UTI indication from suspension NDA. |
| 06/25/93 | Memo from FDA | Request by Leissa for specific gravities on Cefaclor and Ceftibuten. Overview of drug compliance for C88-082/I88-115. |

| | | |
|----------|---------------------------|---|
| 07/07/93 | Letter to FDA | Submission of algorithm for "crossover otitis" as requested by Dr. Leissa 5/6/92. |
| 07/09/93 | Letter to FDA | Paradox script files unrelated to any specific aspect of Cedax. |
| 07/19/93 | Letter from FDA | NDA review extended 180 days to December 16, 1993. |
| 07/22/93 | Letter to FDA | Per June 25, 1993 request from Dr. Leissa enclosed - overview of compliance checks for C88-082/I88-115, C87-112 and C88-065. |
| 07/30/93 | Internal Memo | Summary of a phone call by Mr. Taylor with request to borrow a 15 cm system 1 HPLC column used in analysis of Ceftibuten related compounds. The column was sent by Mr. Guazzo on August 2 (letter attached). |
| 08/02/93 | Letter and package to FDA | HPLC column requested by FDA on 07/30/93 phone call. |
| 08/12/93 | Letter to FDA | Response to Leissa's 6/1/93 E-mail requesting micro response to C90-886. |
| 08/14/93 | Memo from FDA | Dr. Leissa's request for the remaining data for C90-886. |
| 09/09/93 | Letter to FDA | Submission of C90-886 remaining data for 147 reaming patients. |
| 09/10/93 | Internal Memo | Summary of a phone Discussion with Dr. Leissa regarding Ceftibuten suspension review. He described reasons for his delay and gave new projected dates. |
| 10/05/93 | Letter to FDA | Submission of FOI version of suspension EA. submission of summary table of data for confidential EA. submission of minor changes to manufacturing procedures. |
| 11/02/93 | Letter to FDA | Field copy of submission dated 11/02/93 to division of anti-infective drug products regarding alternative drug substance intermediate sourcing. |
| 11/02/93 | Letter to FDA | Amendment, drug substance intermediate sourcing. Notification to the NDA of concurrent amendment to NDA 50-685 for Cedax capsules providing for alternative suppliers of the intermediate 3 alcohol VII. Attached amendments to confidential and FOI version of environmental assessment. |
| 11/09/93 | Letter to FDA | Submission of correction to pharyngitis data originally submitted January and March 1993. |

| | | |
|----------|-----------------|---|
| 12/01/93 | Internal Memo | Summary of phone conversation with C. DeBellas Preliminary review of suspension FPL: Leissa Temporarily assigned to another project; we will resume in mid Dec'93. |
| 12/01/93 | Letter to FDA | Submission of Ceftibuten Drug Substance. |
| 12/09/93 | Memo to FDA | Ceftibuten CFR monograph gentamicin sulfate reference std. |
| 12/09/93 | Internal Memo | Summary of a phone conversation with Leissa: Discussed Ceftibuten suspension review status; Leissa will resume review on 12/10/93. |
| 12/13/93 | Letter to FDA | Pre-approval submission of FPL for discussion. |
| 12/13/93 | Memo from FDA | Question on our 1/20/93 submission on pharyngitis PT number 88-112-02-002. |
| 12/15/93 | Memo from FDA | Calculation of prescribed daily dose. What was done for patients who were given pen V at a Conc. of 25 mg/ml of 100 mg/ml. |
| 12/16/93 | Internal Memo | Summary of a phone Discussion on Ceftibuten suspension NDA review. Carmen Debellas (CSO) told us that we will have Dr. Leissa as the reviewer until he completes the suspension NDA. |
| 12/23/93 | Letter to FDA | Response to Brad Leissa's E-mails of 12/13 and 12/15/93 concerning the 1/20/93 submission of the pharyngitic corrections. |
| 12/28/93 | E-mail from FDA | Request for international marketing update concerning indications V dosage. |
| 12/29/93 | E-mail from FDA | Are Schering findings concerning on adequately presented by Leissa to division. |
| 01/07/94 | Internal Memo | Summary of a phone call to C. DeBellas, The new medical reviewer officer Cedax, Dr. Janice Soreth, will pick up the review of the capsule NDA and has started looking at the bronchitis amendment of 11/15/93. Plans are underway to meet with her. |
| 01/17/94 | Letter to FDA | Response to Dr. Leissa's 12-28-93 E-mail regarding the status of the international market for Ceftibuten suspension. |
| 01/18/94 | Memo to FDA | Cedax suspension review targeted for completion by end of 1-94. Expect action letter by end of 2-94. |

| | | |
|----------|---------------------|--|
| 01/19/94 | Memo from FDA | C90-886 where are demographics and efficacy tables in the October 1992 submission? |
| 01/21/94 | Memo to FDA | Discussion of Leissa's E-mails of 1/19/94 and 12/29/93 overall results. |
| 01/23/94 | Memo from FDA | C90-037: how was diagnosis of EBV infection determined in patient with increased SGOT and SGPT (diagnosed with mononucleosis). |
| 01/24/94 | Letter to FDA | Dr. Taglietti's response to Dr. Leissa's E-mail of 12-29-93 regarding summary of findings of acute otitis media. |
| 01/24/94 | Memo from FDA | Abbreviations in the data base (X90886) how do LEDR and REDR translate? |
| 01/25/94 | Letter to FDA | Response to Dr. Leissa's E-mail of 1-19-94 requesting demographics and efficacy tables for C90-886. Included: summary tables for adverse events, deaths and lab values and listings to support the tables. |
| 01/26/94 | Letter to FDA | Word Perfect copy of our letter of 1-24-94 containing Dr. Taglietti's response to E-mail dated 12/29/93. |
| 01/29/94 | Memo from FDA | Pharyngitis issues related to C87-112. |
| 01/30/94 | Memo from FDA | More pharyngitis issues related to C87-112. |
| 02/02/94 | Memo from FDA | Otitis Media evaluation windows. |
| 02/10/94 | Internal Memo | Summary of phone call to C. DeBellas regarding status of suspension review. |
| 02/14/94 | Letter to FDA | International labeling and translations for Sweden, Spain and Germany. |
| 02/17/94 | Fax letter from FDA | Biopharmaceutics suspension - 2 additional deficiency issues: originally overlooked by CSO. |
| 02/22/94 | Fax letter from FDA | Summary by FDA of 2/21/94 phone call regarding Additional questions concerning EA's for Cedax caps/suspension. |
| 02/22/94 | Fax letter from FDA | Evaluation - windows of the pharyngitis trials C87-11206037. |
| 02/22/94 | Letter from FDA | Approval of methods validation. Also, requested comments on monographs; as well as material for establishment of a master and working standard. |
| 02/23/94 | Fax letter from FDA | More evalualulity of "windows" patient C8711209053. |

| | | |
|----------|---------------------|--|
| 02/24/94 | Fax letter from FDA | Queries regarding clinical and bacteriologic outcomes at EOT and EXT in pharyngitis studies. |
| 02/25/94 | Internal Memo | Summary of a call made to Dr. Leissa to discuss his 2/22/94 and 2/23 and 2/24/94 E-mails. Also present for the call were Drs. Garanud and Tagletti. The discussion related to how the criteria for the micro and clinical EOT and EXT were determined. |
| 02/26/94 | Memo from FDA | Additional point concerning C87-112090-53. |
| 02/27/94 | Memo to FDA | Follow up E-mail dated 2/26/94 on micro/clinical response. Who assigned clinical and Bacteriologic responses at EOT/EXT for pharyngitis? Inadvertently sent directly to Brad Leissa from Marco Taglietti. |
| 02/28/94 | Letter to FDA | Responses to FDA fax of 02/24/94 concerning the environment assessment. (suspension). |
| 03/04/94 | Letter from FDA | Follow up: Brad Leissa is awaiting responses to 2/2/94 E-mail regarding evaluation windows. |
| 03/04/94 | Letter to FDA | Responses to pharyngitis issues in FDA E-mails of 2/22/94, 2/23/94, 2/24/94, 2/26/94. |
| 03/07/94 | Fax letter from FDA | Memorandum of a 03/07/94 telephone conversation regarding FOI copy of environmental assessments. |
| 03/09/94 | Letter to FDA | Response to question #11 and #14 in our FDA 02/17/94 Fax; Question #11 was question #4 in our 3-2-94 submission. |
| 03/21/94 | Letter to FDA | Draft non-confidential environment assessment (revised) submission per Dr. Tso's request to combine original NC EA with amendment. |
| 03/21/94 | Internal Memo | Summary of a phone call to FDA regarding status of Ceftibuten suspension review. Otitis media issue deals with weakness against S. Pneumo. |
| 03/23/94 | Letter to FDA | Non-confidential environmental assessment revised with comments from Dr. Sutso fax of 03/07/94 and conversation of 03/22/94. |
| 03/26/94 | Letter from FDA | From Brad Leissa - Biotyping. |
| 03/26/94 | Letter from FDA | From Brad Leissa: Patient C8711219006 bacteriologic response? |

| | | |
|----------|---------------------|--|
| 03/28/94 | Letter to FDA | Letter to Mr. David Moss containing responses to questions regarding a loaner of PC equipment and software to Dr. Janice Soreth. This is in accordance to Canada guidelines; letter is their template. |
| 03/29/94 | Letter to FDA | To Brad Leissa regarding phone conversation with Dr. Taglietti on 03/28/94. Confirmation of patient availability. |
| 04/04/94 | Fax letter from FDA | From Dr. Soreth: Canada shipment arrived. |
| 04/14/94 | Letter to FDA | Documents and computer disk sent to Dr. Soreth regarding installation of Paradox. |
| 05/19/94 | Letter to FDA | Submission of comments to Draft CFR monographs for Cefitibuten substance dosage forms. Also, confirm as of submission of substance to develop standards. |
| 06/01/94 | Fax letter from FDA | From Pere Dionne: regarding monographs sent to FDA on 05/19/94 approved with minor comments. |
| 07/12/94 | Memo to FDA | Change of Cedax suspension name regarding dosage form per FDA revision regarding of non-confidential ET. |
| 07/22/94 | Fax letter from FDA | Two Questions re: MIC's for H-flu and strep.pneum. Request EA deleting "powder" from suspension. |
| 07/25/94 | Letter to FDA | Safety Update Report. |
| 07/25/94 | Letter to FDA | Non Confidential environmental assessment revised to remove the word "powder" from the product name. |
| 07/25/94 | Letter to FDA | Information Amendment: Clinical Safety Synopsis for C90-047. |
| 07/25/94 | Letter from FDA | Re: Receipt of Cefitibuten to create Std. Analyzed & Assigned Potency Officially. |
| 07/29/94 | Letter to FDA | Requesting meeting w/FDA discussing short term therapy program for Cedax Capsule & Suspension. |
| 07/29/94 | Memo | Follow up to August meeting. People needed are dedicating time to Cedax NDA's review. |
| 08/02/94 | Memo | Discussed review status of NDA; CDMP 92-107, short term therapy, & Sept. meeting. |
| 08/08/94 | Fax letter from FDA | Scheduling of Cedax meeting with FDA for 09/29/94 at 10:45 am. |
| 08/09/94 | Letter to FDA | Response to FDA fax (7/22/94) from Carmen Debellas, CSO regarding microbiological testing H-inf & S. Pneum. |

| | | |
|----------|---------------------|--|
| 08/09/94 | Fax letter from FDA | Correction of Ceftibuten Substance Monograph Numbers from Valerie Flournoy. |
| 08/12/94 | Fax letter from FDA | Request to Reformat the Adverse Reaction Section of Package Insert (from Carmen Debellas). |
| 08/22/94 | Letter to FDA | Disk Containing Reformatted Adverse Reaction Section of Package Inserts. (Referring to 8-12-94 request) |
| 09/02/94 | Memo | Discussion on status of Cedax Suspension Review & Antral Puncture vs. Endoscopy for Sinusitis Program. |
| 09/29/94 | Meeting with FDA | CEDAX oral suspension NDA. |
| 11/21/94 | Letter to FDA | 11-29-94 Meeting Agenda enclosed with 2 Protocols for study of 5-day therapy in acute otitis media. |
| 11/23/94 | Memo | Discussion between Carmen & Lumpkin on Pharm Study; Labels/Cartons; PI's; & ADR's. Packages also returned. |
| 11/28/94 | Memo | Considering arrangements for a preliminary "date" for labeling meeting. |
| 11/29/94 | Meeting with FDA | CEDAX oral suspension protocols for use in short term therapy. |
| 12/29/94 | Letter from FDA | Approvable Letter for our 12/20/91 New Drug Applications. |
| 01/03/95 | Letter to FDA | Re: 12-29-94 letter, 2 applications approved. Need additional info & meeting. |
| 01/03/95 | Letter to FDA | Meeting Minutes on 11/29/94 discussing usage of Cedax in short term therapy. |
| 01/04/95 | Internal Memo | Summary of phone Conversation w/Carmen on FDA letter: item 8. (international labeling, translations, additional study) |
| 01/06/95 | Memo | Question on PI; missing micro data; sucrose formulation; discussion w/Renata & Janice on S. Pneum. in Europe (#6). |
| 01/10/95 | Memo | Agreement to send M. Cat Data in w/draft PI to support AECB in 1 complete package. |
| 01/12/95 | Internal Memo | Summary of phone Conversation w/Carmen re: 045 study. Exploring dates for future conference. |
| 01/13/95 | Internal Memo | Summary of phone Discussion w/Carmen re: otitis media. Corrections needed for future review. |
| 02/02/95 | Letter to FDA | Outline of 5 items for Dr. Soreth's teleconference on 2-3-95. |

| | | |
|----------|----------------------------|---|
| 02/02/95 | Letter from FDA | Medical Officer's Review of NDA 50-686 |
| 02/03/95 | Memo to FDA | Discussed the five issues identified in the approvability letter of 12/29/94. |
| 03/07/95 | Letter to FDA | Requesting meeting w/Lumpkin to discuss Cedax Suspension/Capsule proposed labeling. Agenda submitted. |
| 04/27/95 | Letter to FDA | Agenda letter for 5-12-95 meeting on acute otitis media & acute bacterial exacerbation of chronic bronchitis. |
| 05/02/95 | Letter to FDA | Response to approvability letter of 12/29/94 |
| 05/12/95 | Meeting with FDA | Acute otitis media and acute bacterial exacerbation of chronic bronchitis. |
| 05/15/95 | Internal Memo | Minutes of 5/12/95 FDA Meeting Re: Cedax |
| 05/18/95 | Letter to FDA | Summary of Cedax PI. |
| 06/20/95 | Letter to FDA | Enclosed flat color copy of main panel of Cedax compliance kit for review. Included in pre-approval launch to DDMAC. |
| 06/23/95 | Letter to FDA | Labeling |
| 06/26/95 | Tele-conference with FDA | Compliance Kit for CEDAX |
| 07/07/95 | Memo to FDA | Summary of call by Dr. Giaquinto to Dr. Lumpkin per the Cedax Labeling sent to the FDA on 6/23/95. |
| 07/17/95 | Letter to FDA | Responsive to 06/26/95 Teleconference Labeling agreement |
| 08/02/95 | Memo | Verification of requirements to implement use of a new warehouse for Cedax related activities. |
| 08/10/95 | Letter to FDA | Submitted the logo for Cedax Oral Suspension for review. |
| 08/16/95 | Letter to FDA | Submitted replacement pages for clinical study report C88/082/I88-115 previously submitted to FDA on 10/19/92. |
| 09/07/95 | Approvable Letter from FDA | Asked to revise our labeling package and submit draft labeling that is identical to the enclosed labeling date 9/7/95. |
| 09/11/95 | Letter to FDA | Letter notifying FDA of our intent to provide the requested information required for the approval of the NDA's |
| 09/12/95 | Tele-conference with FDA | Discussions with FDA regarding CEDAX Labelling. |
| 09/13/95 | Letter to FDA | Following a teleconference of 9/12/95, suggested that a meeting be set up to discuss the labeling proposed in the letter of 9/7/95. |

| | | |
|----------|------------------|---|
| 10/23/95 | Letter to FDA | Pursuant to a 10/13/95 phone conversation, meeting at FDA planned for 11/14/95 at 4 p.m. |
| 11/14/95 | Meeting with FDA | CEDAX Labelling. |
| 11/20/95 | Letter to FDA | Submission of final draft Cedax PI |
| 12/07/95 | Letter to FDA | Proposed Journal ads for Cedax Capsules/Suspension. |
| 12/18/95 | Memo | Follow-up with Mr. DeBellas to discuss labeling issues |
| 12/20/95 | Approval Letter | CEDAX (Ceftibuten for Oral suspension) NDA. |
| 12/20/95 | Letter to FDA | Letter of confirmation of labeling for both Cedax Suspension/Capsules |
| 12/27/95 | Letter to FDA | Proposed promotional and advertising materials. |
| 01/04/96 | Letter to FDA | Per FDA approval letter of 12/20/95, enclosed were 15 copies of the final printed package insert. |

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

-----X
In re: United States Patent :
No. 4,634,697 :

Attn: Box Patent Ext.

Inventor: Yoshio Hamashima :

Issue Date: January 6, 1987 :
-----X

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

#15
RECEIVED
FEB 12 1996
OFFICE OF PETITIONS
AND PATENTS

REQUEST FOR EXTENSION OF PATENT TERM UNDER
35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.785,
Schering Corporation ("Schering"), authorized agent (see Exhibit I) for
Shionogi & Co., Ltd. ("Shionogi"), owner of the above-identified patent by
virtue of an Assignment by Yoshio Hamashima of his interests in the above-
identified patent which was executed on March 7, 1985 and recorded in the
United States Patent and Trademark Office ("USPTO") on March 12, 1985 at
Reel: 4383, Frames: 0597 to 0598 (Exhibit IX) hereby requests an
extension of the 20 year from filing date patent term set pursuant to 35

P 30051 U.S.C. §154(c)(1) of United States Patent No. 4,634,697.¹
02/13/96 4634697

19-0365 030 111 1,060.00CH

¹This request is proper under the October 16, 1995 Memorandum Opinion in Merck et al., U.S. District Court for the Eastern District of Virginia, Consolidated Nos. 95-CV-1005 et al. Schering recognizes that the Commissioner of Patents and Trademarks, the Commissioner of Food and Drugs, and the Generic Pharmaceutical Industry Association ("GPIA") have appealed to the United States Court of Appeals for the Federal Circuit to reverse the District Court's decision. Merck v. Kessler, Fed. Cir. Nos. 96-1108 et al. If the Federal Circuit adopts the position advanced in that case by the Commissioner of Patents and Trademarks and the Commissioner of Food and Drugs, then Schering requests an extension of the 17 year from issue term of United States Patent No. 4,364,697. If the Federal Circuit adopts the position advanced in that case by the Generic Pharmaceutical Industry Association in that case, then there is no need for Schering to change its request for

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.785 and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAMES, PHYSICAL STRUCTURE OR CHARACTERISTICS:

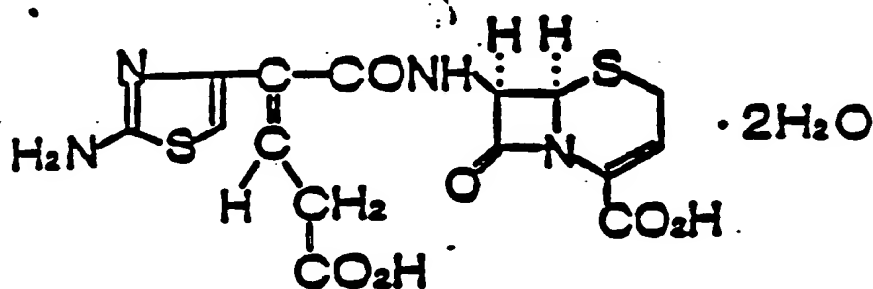
The approved product is CEDAX® (Ceftibuten capsules). As used herein, the chemical name for the active ingredient in the approved product is ceftibuten which is present in the approved product as ceftibuten dihydrate. The active ingredient in the approved product has the following generic and chemical names and structural formula:

| | |
|----------------------|--|
| Generic Name: | Ceftibuten/Ceftibuten dihydrate |
| Code Designations: | 7432-S (Shionogi); and Sch 39720 (Schering) |
| CAS Registry Number: | CAS 97519-39-6 |
| Chemical Names; | |
| (1) | 5-Thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-, [6R-[6 α ,7 β (Z)]]], dihydrate |

extension of the 20 year from filing term of United States Patent No. 4,364,697. Schering explicitly reserves the right to seek reconsideration and review of a USPTO determination to grant an extension of the 17 year from issue date term.

- (2) (+)-(6R,7R)-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, dihydrate.
- (3) 7B-[(Z)-2-(2-Aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid, dihydrate

Structural Formula



(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The regulatory review occurred under §507 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 357. Section 507 of FFDCA provides for the submission and approval of new drug applications ("NDAs") for antibiotic drug products meeting the definition of "antibiotic drug" under §507 of the FFDCA, 21USC §357(a)

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

CEDAX® (ceftibuten capsules) were approved by the FDA for commercial marketing on December 20, 1995 for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis in humans. (See Exhibits VII and VIII)

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT OR THE VIRUS-SERUM TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The active ingredient in the approved product, CEDAX® (ceftibuten capsules), has the generic name of ceftibuten and the chemical names listed in Paragraph No. (1) herein above as well as in Exhibits II and VIII. The active ingredient, ceftibuten, approved for marketing under Section 507 of the FFDCA, has not previously been approved for commercial marketing or use under the FFDCA, The Public Health Service Act or the Virus-Serum Toxin Act.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SEC. 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

The product was approved on December 20, 1995, and the last day within the sixty day period permitted for submission of an application for extension of the relevant U.S. Patent is February 18, 1996. February 18, 1996 is a Sunday and submission of this application is considered timely filed if submitted on or before February 20, 1996. This application is being timely filed before the expiration of the February 20, 1996 deadline, pursuant to 35 USC §21(a) and (b) and 37 CFR §1.7 and 1.741(a).

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO. 4,634,697

INVENTOR: YOSHIO HAMASHIMA

DATE OF ISSUE: JANUARY 6, 1987

FILING DATE: OCTOBER 1, 1984

EXPIRATION DATE: OCTOBER 1, 2004

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS), AND DRAWINGS:

A copy of the patent is attached as Exhibit III.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers or certificates of correction were filed for U.S. Patent No. 4,634,697. United States Patent No. 4,634,697, has not been re-examined and, as such, no re-examination certificate has been issued.

A copy of the receipt of the first maintenance fee statement (mailing date July 17, 1990) is attached as Exhibit XA. A copy of the second maintenance fee statement (mailing date May 6, 1994) paid on April 18, 1994 by Shionogi and good through January 6, 1998 is attached hereto as Exhibit XB.

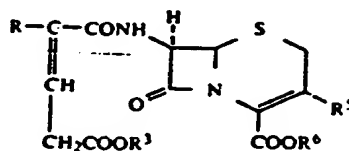
(9) A STATEMENT THAT THE PATENT CLAIMS, THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

Claims 1-3, 17 and 18 of United States Patent No. 4,634,697 read on CEDAX® (ceftibuten capsules) for the FDA approved indication for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media, pharyngitis and tonsillitis. See the paragraphs in the Product Information Sheet entitled "Description" (upper left hand column

and "Dosage and Administration" (upper right hand column) and "Indications and Usage" (lower right hand column) (Exhibit VIII).

Claim 1 of United States Patent No. 4,634,697 reads

A compound of the formula



wherein

R is 2-aminothiazol-4-yl the amino group of which is unprotected or protected with a protecting group,

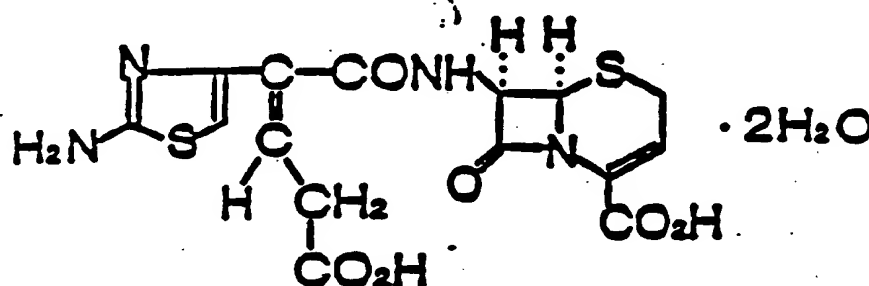
R³ is (1) hydrogen, (2) a pharmacologically acceptable salt forming group, (3) phthalidyl, (4) phenacyl, (5) C₂₋₇alkenyl, (6) diphenylmethyl, (7) trityl, (8) phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy or (9) a lower alkyl group,

R⁵ is hydrogen, methyl, vinyl, cyanovinyl, trifluoropropenyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, thiadiazolylthiomethyl, triazolylthiomethyl, aminomethylthiadiazolylthiomethyl, aminothiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio, or halogen, and

R⁶ is (1) hydrogen, (2) a pharmacologically acceptable salt forming atom or group, (3) a lower alkyl group, (4) a lower alkenyl group (5) phthalidyl, (6) phenacyl, (7) diphenylmethyl, (8) trityl or (9)

phenylalkyl of 7 to 15 carbon atoms said group being unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 2 carbon atoms, nitro, amino or hydroxy.

The below-listed structural formula for ceftibuten dihydrate, the active ingredient in CEDAX[®] (Ceftibuten capsules) is set forth in paragraph 1 (page 2) herein above and on page 1, of Exhibit VII.) See also Product Information Exhibit VIII upper left hand column.



Thus claim 1 covers ceftibuten and ceftibuten dihydrate wherein R³, R⁵ and R⁶ are each hydrogen and R is 2-aminothiazol-4-yl, the amino group of which is unprotected.

Claim 2 reads:

A compound according to claim 1 wherein

R³ is hydrogen or a pharmacologically acceptable salt forming group,

R⁵ is hydrogen, methyl, vinyl, trifluoropropenyl, methoxymethyl,

carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl,

thiadiazolylthiomethyl, methoxy, fluoroethylthio, trifluoroethylthio,

or halogen, and

R⁶ is hydrogen or a pharmacologically acceptable salt

forming atom or group.

Thus, claim 2 covers ceftibuten and ceftibuten dihydrate wherein R³, R⁵ and R⁶ are each hydrogen.

Claim 3 reads:

A compound according to claim 1, said compound being 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid.

Claim 3 specifically covers ceftibuten and ceftibuten dihydrate. See chemical names in paragraph 1 herein above, and specifically chemical name (3).

Claim 17 reads:

An antibacterial composition which comprises an antibacterially effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier therefor.

Claim 17 covers ceftibuten and ceftibuten dihydrate for reasons stated in reference to claim 1 and in that the CEDAX® (Ceftibuten capsules) is a pharmaceutical composition approved by the FDA for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis each of which are due to bacterial agents. See Product Information Sheet under paragraphs entitled "Dosage and Administration" and "Indications and Usage" (right hand column) of Exhibit VIII.

Claim 18 reads:

**A method for combating bacteria which comprises
bringing an antibacterially effective amount of a
compound of claim 1 into contact with the bacteria.**

**Claim 18 covers ceftibuten and ceftibuten dihydrate for the reasons stated in
reference to claims 1 and 17.**

(10) A STATEMENT BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A NEW DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

Schering of Kenilworth, New Jersey is the authorized agent of Shionogi by virtue of the appointment of agent (Exhibit I) to Schering. Shionogi is the assignee of record of United States Patent No. 4,634,697 by virtue of the Assignment dated March 7, 1985 by Yoshio Hamashima of his interest in U.S. Patent No. 4,634,697 (Exhibit IX) recorded in the USPTO on March 12, 1985 at REEL: 4383, FRAMES: 0597 to 0598.

In furtherance of the need for an approved NDA, Schering, on June 30, 1987 submitted to the FDA, a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under §505 of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent NDA for the use of CEDAX® (Ceftibuten capsules) in humans. The Schering

letter transmitting the IND to the FDA is attached as Exhibit IV. By a letter dated July 7, 1987, the FDA acknowledged receipt of the IND and assigned the IND No. 30,303. A copy of this FDA letter is attached as Exhibit V. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) as August 2, 1987, the effective date of an investigational exemption under §505 of the FFDCA.

Schering submitted a New Drug Application (NDA) for CEDAX® (Ceftibuten capsules) in humans on December 20, 1991. A copy of this Schering letter transmitting the NDA is attached as Exhibit VIa. By a letter dated January 7, 1992, the FDA acknowledged receipt of the NDA submission dated December 20, 1991 and assigned the submission NDA No. 50-685. A copy of this FDA letter is attached as Exhibit VIb.

By a letter dated December 20, 1995 (copy attached as Exhibit VII) the FDA advised Schering that the NDA No. 50-685 for use of CEDAX® (Ceftibuten capsules) in humans for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis in humans was approved effective on December 20, 1995.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i), the "testing phase" began on August 2, 1987, the date of the IND No. 30,303 effective and ended on December 20, 1991, the date the NDA No. 50-685 was initially submitted by Schering for use of CEDAX® (Ceftibuten capsules) in humans under §505 of the FFDCA. And, for purposes of determining the "approval phase" of the "regulatory review period" under 35 U.S.C.

§156(g)(1)(B)(ii) the "approval phase" began on December 20, 1991, the date the NDA No. 50-685 was initially submitted by Schering to the FDA and ended on December 20, 1995, the date on which the NDA No. 50-685 was approved by the FDA.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE ACTIVITIES UNDERTAKEN BY SCHERING, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

During the applicable regulatory review period, Schering was actively involved in obtaining FDA approval for the use of ceftibuten capsules for the treatment of acute bronchitis and acute exacerbations of chronic bronchitis and urinary tract infections in humans. As previously noted, Schering submitted an IND on June 30, 1987 and in close consultation with the FDA conducted clinical trials from August 2, 1987 through December 20, 1991 under IND No. 30-303. Schering submitted on December 20, 1991 NDA No. 50-685 for the use of CEDAX® (Ceftibuten capsules) for the treatment of acute bronchitis and acute exacerbations of chronic bronchitis and urinary tract infections in humans. From December 20, 1991 to December 20, 1995 Schering continued to interact with various FDA officials and answered numerous questions, generated requested data and supplied requested information regarding all clinical studies and data on the use of CEDAX® (Ceftibuten capsules) for the treatment of acute bronchitis and acute exacerbations of chronic bronchitis and urinary tract infections in humans worldwide to obtain health approval. A brief description of the significant activities undertaken by Schering with respect to the use of CEDAX® (Ceftibuten capsules) for the treatment of acute bronchitis and acute exacerbations of chronic bronchitis and urinary tract infections in humans during the regulatory review period is set forth in Exhibit XI (IND) and Exhibit XII (NDA) and is illustrative of the activities involved.

(12) A STATEMENT BEGINNING ON A NEW PARAGRAPH THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR AN EXTENSION AND A STATEMENT AS TO THE LENGTH OF THE EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in the relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 USC §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Publ. 103-465, 108 Stat.

4809 (1994) and 35 U.S.C. §156, the term of United States Patent No. 4,634,697 currently expires on October 1, 2004. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 4,634,697.

(2) The term of this patent has never been extended under 35 U.S.C §156(e)(1).

(3) This application is being submitted by Schering Corporation, by virtue of the appointment of agent to Schering Corporation by Shionogi, the owner of record of this patent (Exhibit I). Shionogi is the owner of record by virtue of the Assignment by Yoshio Hamashima of his interest which was recorded in the USPTO on March 12, 1985 at Reel: 4383, Frames: 0597 to 0598 (copy attached as Exhibit IX). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on December 20, 1995, the date the product received permission for marketing under the FFDCA and ending on February 20, 1996 and contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 20, 1995 letter from the FDA (Exhibit VII), to Schering-Plough Corporation (of which Schering Corporation is a wholly owned subsidiary), the product was subject to a regulatory review period under §507 of the FFDCA before its commercial marketing or use.

(5) Finally, the CEDAX® (Ceftibuten capsules) product was approved by the FDA for treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media and pharyngitis and tonsillitis.

The permission for the commercial marketing of CEDAX® (Ceftibuten capsules) after regulatory review under §507 of FFDCA, 21 U.S.C. §357, is the first permitted commercial marketing and use under §507 for humans of the active ingredient ceftibuten in CEDAX® (Ceftibuten capsules). This is confirmed by the absence of any approved new drug application for the active ingredient in humans prior to December 20, 1995.

(b) Statement as to length of extension claimed:

The 20 year from filing term of United States Patent No. 4,634,697 now expiring on October 1, 2004 should be extended by 1,826 days (5 years). This extension was determined on the following basis. As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of the IND No. 30,303 of August 2, 1987 and the submission of the NDA on December 20, 1991 a period of 1,602 days, plus the length of time between the submission of the NDA on December 20, 1991 to NDA approval on December 20, 1995, a period of 1,461 days. These two periods added together equal 3,063 days.

Pursuant to the introduction of 35 U.S.C. §156(c), the term of the patent eligible for extension shall be extended only for that portion of the regulatory review period which occurs after the date the patent is issued. In this case, no limitation under the introduction to §156(c) applies in that the issue date of United States Patent No. 4,634,697 (January 6, 1987) is before the date on which the regulatory review period began.

Section 156(c)(2), requires the period calculated under §156(g)(1)(B)(i) to be reduced by one-half of the 1,602 day period; this reduction results in a value of 801 days.

From the foregoing calculation, an extension of 2,262 days results, i.e., the period under 35 U.S.C. 156(g)(1)(B)(i) as limited by §156(c)(2) (801 days) plus the period under 35 U.S.C. 156(g)(1)(B)(ii) (1,461 days). This extension period is subject to two further potential limitations under §156.

First, under §156(g)(6)(A), a maximum extension of five years is permitted. Since the calculated extension (2,262 days) is more than five years (1,827 days), this limitation does apply (the patent issued on January 6, 1987, which was after the enactment of §156 in 1984).

Second, under §156(c)(3), if the period remaining in the term of the patent after the date of approval, that is, December 20, 1995, to October 1, 2004, when added to the extension period calculated above would exceed 14 years, the period of extension would be limited so that the total does not exceed 14 years. In this case, however, the total of the remaining term (3,209 days) plus the five year extension (1,826 days) is 5,036 days and does not exceed the 14 year (5113 days) limit, and the extension is not reduced.

Accordingly, United States Patent No. 4,634,697 is eligible for 5 year or a 1,826 day extension from October 1, 2004 to October 1, 2009.

Schering's request for extension of term of 20 years from application filing date for United States Patent No. 4,634,697 is proper under the

October 16, 1995 Memorandum Opinion in Merck et al., v. Kessler et al., U.S. District Court for the Eastern District of Virginia, Consolidated Nos. 95-CV-1005 et al. Schering recognizes that the Commissioner of Patents and Trademarks, the Commissioner of Food and Drugs, and the Generic Pharmaceutical Industry Association ("GPIA") have appealed to the United States Court of Appeals for the Federal Circuit to reverse the District Court's decision. Merck v. Kessler, Fed. Cir. Nos. 96-1108 et al. If the Federal Circuit adopts the position advanced in that case by the Commissioner of Patents and Trademarks and the Commissioner of Food and Drugs, then Schering requests an extension of the 17 year from issue term of United States Patent No. 4,634,697. In that event, United States Patent No. 4,634,697 would be eligible for a five year (1827 day) extension from January 6, 2004 to January 6, 2009.

(13) A STATEMENT ON A NEW PAGE THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

Schering acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

As stated in Paragraph No. (9) herein above, Schering asserts that claims 1-3, 17 and 18 of United States Patent No. 4,634,697 embrace the approved product, the CEDAX® (ceftibuten capsules) and its use for the approved indication and usage of said approved product.

The term of United States Patent No. 4,634,697 has never been extended. A copy of this patent is attached as Exhibit III.

(14) PRESCRIBED FEES:

The Commissioner is authorized to charge our Deposit Account No. 19-0365 in the amount of \$1,060.00 or any other fee necessary for this application to prevent it from becoming inadvertently abandoned.

(15) THE NAME, ADDRESS AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THIS APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED TO:

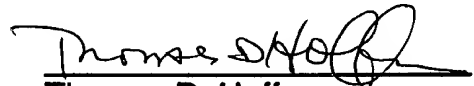
THOMAS D. HOFFMAN
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1- 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NEW JERSEY 07033-0530
TEL. NO. (908) 298-5037
FACSIMILE NO. (908) 298-5388

**(16) CERTIFICATION THAT THE ENCLOSED DUPLICATE COPY
OF THIS APPLICATION IS A TRUE COPY OF THE ORIGINAL:**

I, Thomas D. Hoffman, Registration No. 28,221, as duly appointed attorney (by virtue of the following Power of Attorney duly executed by James R. Nelson, Vice President for Schering Corporation) for Applicant, Schering Corporation, authorized agent (by virtue of the Appointment of Agent, see Exhibit I) for the owner of record of United States Patent No. 4,812,561 (by virtue of the aforesaid Assignment, see Exhibit (IX) which has applied for an extension of term of this patent, declare that duplicate copy of this application transmitted herewith is a true copy of the original application.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of United States Patent No. 4,812,561.

Date: 02/09/96


Thomas D. Hoffman
Attorney for Authorized Agent
Registration No. 28221
Tel. No. (908) 298-5037

**DECLARATION AND POWER OF ATTORNEY
BY AUTHORIZED AGENT**

As the below identified official of Schering Corporation, the authorized agent for the owner of record of United States Patent No. 4,634,697, which has applied for an extension of term of this patent, I declare (1) that I have been authorized to practice before the United States Patent and Trademark Office; and (2) that I have general authority from Schering Corporation, the authorized agent of the owner of record, to act on behalf of the owner of record in patent matters.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and United States Patent No. 4,634,697.

POWER OF ATTORNEY: I hereby appoint as United States attorneys and with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Thomas D. Hoffman, Reg. No. 28,221; John J. Maitner, Reg. No. 25,636; Norman C. Dulak, Reg. No. 31,608; Edward H. Mazer, Reg. No. 27,573; Eric S. Dicker, Reg. No. 31,699, and Richard J. Grochala, Reg. No. 31,518.

Send correspondence to:

Thomas D. Hoffman
Schering-Plough Corporation
Patent Dept., K-6-1-1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
Tel. No. (908) 298-5037

Date: February 9, 1996

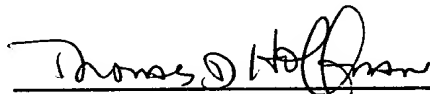
By: James R. Nelson
James R. Nelson
Vice President,
Schering Corporation
Reg. No. 27,929

(17) DECLARATION FOR EXTENSION OF UNITED
STATES PATENT NO. 4,634,697

I, THOMAS D. HOFFMAN, Registration No. 28,221, as duly appointed attorney (by virtue of the Power of Attorney duly executed by James R. Nelson, Vice President for Schering Corporation) for Applicant, Schering Corporation, the authorized agent for Shionogi (virtue of the Appointment of Agent, See Exhibit I), the owner of record of United States Patent No. 4,634,697 (by virtue of the aforesaid Assignment, see Exhibit IX) which has applied for an extension of term of this patent, declare(1) that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,634,697; (2) that I believe that the patent is subject to extension under 35 U.S.C. §156 and 37 C.F.R. §1.710; (3) that I believe that the length of extension claimed for the 20 year from filing date term specified in paragraph 12(A) is fully justified pursuant to 35 USC §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Publ. 103-465, 108 Stat. 4809 (1994) and 35 U.S.C. §156 and the applicable regulations; and (4) that I believe that the patent for which an extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156 and 37 C.F.R. § 1.720.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of United States Patent No. 4,634,697.

Date: 02/09/96



Thomas D. Hoffman
Attorney for Authorized Agent of Record
Reg. No. 28,221
Tel. No. (908) 298-5068

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

-----X
In re: United States Patent :
No. 4,634,697 :

Attn: Box Patent Ext.

Inventor: Yoshio Hamashima :

Issue Date: January 6, 1987 :
-----X

RECEIVED

FEB 12 1996

**OFFICE OF PETITIONS
AND PATENTS**

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

**LETTER OF TRANSMITTAL OF APPLICATION FOR
EXTENSION OF PATENT TERM**

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,634,697 and a duplicate of the papers thereof, certified as such.

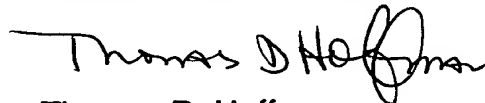
Also submitted herewith is an additional original declaration for extension of U.S. Patent No. 4,634,697. Therefore, the present application is complete and entitled to a filing date of 02/12/96.

Applicant, Schering Corporation ("Schering") states that Schering is the authorized agent for Shionogi and Co., Ltd., ("Shionogi") owner of U.S. Patent No. 4,634,697, (see Exhibit I); that Schering is the holder of the regulatory approval granted with respect to the regulatory review period for CEDAX® (ceftibuten capsules) as evidenced by: (1) submission on June 30, 1987 by Schering of IND No. 30,303 to the Food

and Drug Administration ("FDA") for the purpose of conducting clinical studies for the use of Ceftributen (Sch 39720 oral) oral in humans (see Exhibit IV); (2) the submission on December 20, 1991 by Schering of NDA No. 50-685 for CEDAX® (ceftributen capsules) (see Exhibit VIa); and (3) the FDA letter dated December 20, 1995 approving NDA No. 50-685 for CEDAX® (ceftributen capsules) for the treatment of acute bacterial exacerbations of chronic bronchitis and acute bacterial otitis media and pharyngitis and tonsillitis in humans (see Exhibit VII).

The Commissioner is hereby authorized to charge payment in the amount of \$1,060.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0365. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



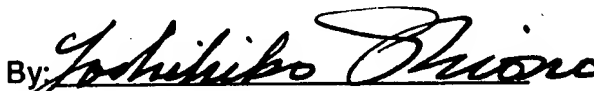
Thomas D. Hoffman
Registration No. 28221
Attorney for Assignee of Record
Telephone No. (908) 298-5037

SCHERING-PLOUGH CORPORATION
Patent Department K-6-1-1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

Now, therefore, as the below-identified official of Shionogi I state that (1) I have been authorized to obligate Shionogi to sign this Appointment of Agent and (2) I hereby appoint Schering, its subsidiaries and/or its designees as agents of Shionogi for the express purpose of submitting and handling all matters and correspondence in the U.S. Patent and Trademark Office attendant to the application for extension of the term of U.S. Patent 4,634,697 covering CEDAX Capsules pursuant to 35 USC §156. This appointment shall be co-extensive with the term of the aforesaid agreement between Shionogi and Schering.

Shionogi & Co., Ltd.

Date: January 18, 1996

By: 

Name: Yoshihiko SHIONO
(type in name)

Title: Representative Director